American Journal of Diseases of Children

VOLUME 58 NOVEMBER 1939 NUMBER 5

COPYRIGHT, 1939, BY THE AMERICAN MEDICAL ASSOCIATION

CONTROL OF IMPETIGO

RANDOLPH G. FLOOD, M.D.

SAN FRANCISCO

It is generally agreed that impetigo in the nursery of the newborn is spread by the attendants' hands. Sauer,[1] describing the spread of a recent epidemic of respiratory infection in the Evanston Cradle, spoke of impetigo as a contact hand infection.

After observing the incidence of impetigo in our own nurseries for the past sixteen years, my associates and I have come to the same conclusion and have decided (1) that there has been a definite correlation between the nursery population and the incidence of the disease, (2) that any nursery procedure which minimizes the handling of the infant also reduces the incidence of impetigo and (3) that the occurrence of the sporadic case is almost unavoidable.

During this time we have altered the technic of the nursery many times, starting with open nursery care and ending with the individual crib procedure. We found that in spite of what we considered good individual technic we still had outbreaks of impetigo. We knew that the infants' environment was sterile, and we thought that the nurses' hands were clean, as cultures of material obtained on swabbing were sterile. At that time the nurses were using hot running water, soft soap and 70 per cent alcohol. In spite of the sterile swabbings obtained from their hands, we were still suspicious of them as a source of infection.

It was brought to our attention that possibly the alcohol was acting as a precipitating factor, depositing a fine film of insoluble soaps or ethylates over the hands. When the swab was passed over this film no growth could be obtained, but when the film was dispersed by traumatization the infants were exposed to the infectious epidermis of the nurses' hands.

To check this hypothesis, after the hands of 6 nurses had been passed through running water, soft soap and 70 per cent alcohol, material was secured by (1) a gentle swabbing of the palmar surface and (2) a heavy swabbing of the same area, by which we endeavored

From the Department of Pediatrics, St. Mary's Hospital.

1. Sauer, L. W., and McDonald, J. J.: A Midsummer Infection in an Aseptically Conducted Adoption Nursery, J. Pediat. **14**:304-306 (March) 1939.

to disrupt the precipitated film and obtain the material from the hand itself. Four of the first swabbings were sterile, and two showed evidence of contamination. All six of the second group of swabbings yielded growth on culture, usually of some form of staphylococcus.

To obtain a more accurate measure of the effectiveness of washing with soap, water and alcohol, the following procedure was followed:

In each of two sterile basins was placed 1,000 cc. of sterile water. To the second basin, or basin B, was added a sterile hand brush. The nurses, after proceeding with the usual water, soap and alcohol technic, were requested to submerge their hands in basin A for one minute, rubbing the hands together, and then to scrub their hands for one minute in basin B to disrupt the precipitated film. One cubic centimeter of water from each basin was then placed in a tube of melted agar and the whole poured into a Petri dish and incubated for thirty-six hours, after which the colonies were counted. The results are tabulated in the accompanying table.

Results of Different Technics of Washing

Washing Procedure	Hot Water and Soft Soap for 2 Minutes	Hot Water and Soft Soap for 2 Minutes and 70% Alcohol for 15 Seconds	5% Dilution of Compound Solution of Iodine U. S. P. for Count of 10 and Sodium Thiosulfate for 5 Seconds
Basin A, colonies per cubic centimeter after one minute soak	488	313	16
Basin B, colonies per cubic centimeter after one minute scrub	Over 5,000	2,130	1,545

From these results it was apparent that the alcohol afforded a semisterile superficial film, which when disrupted exposed the child to contaminated hands. The problem then arose of finding a disinfectant for the hands which would incorporate several characteristics: 1. It should not be detrimental to the nurses' hands. 2. It must have a definite germicidal action. 3. It must not leave a precipitated film on the hands to cover an underlying contaminated field. 4. It must lend itself to practical application.

The first choice was sterile gloves, as recommended in the Dick procedure,[2] in which changing to new gloves for each infant is advocated. This procedure was obviously not practical for a large nursery. There was little to be gained by merely wearing gloves, as they would become contaminated by the infants and the insoluble film could be precipitated on them as on the hands. Further, wet gloves would be slippery, and there was the possibility of dropping the infant.

2. Dick, B. M.; Dick, G. H., and Williams, J. L.: Etiology of an Epidemic of Enteritis Associated with Mastoiditis in Infants, Am. J. Dis. Child. **35**:955-963 (June) 1928.

We first tried a 1:1,000 solution of potassium permanganate ($KMnO_4$), removing the insoluble film with dilute oxalic acid. We found that the nurses could not stand this procedure, and we had many complaints with regard to sore hands and discolored nails.

Our next choice was an iodine preparation which in extremely diluted solutions had had considerable vogue in France as a disinfectant for the skin: compound solution of iodine U. S. P. (Lugol's solution), which is prepared by dissolving 5 Gm. of crystalline iodine and 10 Gm. of potassium iodide in 100 cc. of water. This we diluted to a 5 per cent solution, which gave a 1 per cent solution of iodine and a 1.5 per cent solution of potassium iodide. The hands were first submerged in this solution and then passed through a saturated solution of sodium thiosulfate ($Na_2S_2O_3 + 5H_2O$), which quickly removed the precipitated film and left the hands in a fine velvety condition.

The nurses have been delighted with the procedure, and we have had no complaints; in fact, the girls in the nursery boast the softest hands in the hospital. We have experienced no iodism.

Our procedure is simple. When the nurse reports for duty she has a regular surgical scrub for five minutes before entering the nursery. This is the only soap and water wash that she uses while in the nursery. However, before and after handling any infant she submerges the hands up to the wrists in 5 per cent compound solution of iodine, counting to ten during the procedure. She then places her hands in a basin containing a saturated solution of sodium thiosulfate. The hands are left in this basin until the brown of the iodine has entirely disappeared. This requires about five seconds. She then proceeds to service the infant with wet hands.

In order to compare experimentally the effectiveness of the iodine solution with that of soap and water and of water, soap and alcohol, we had the nurses follow the procedure previously described for the use of water, soap and alcohol before having the initial surgical scrub.

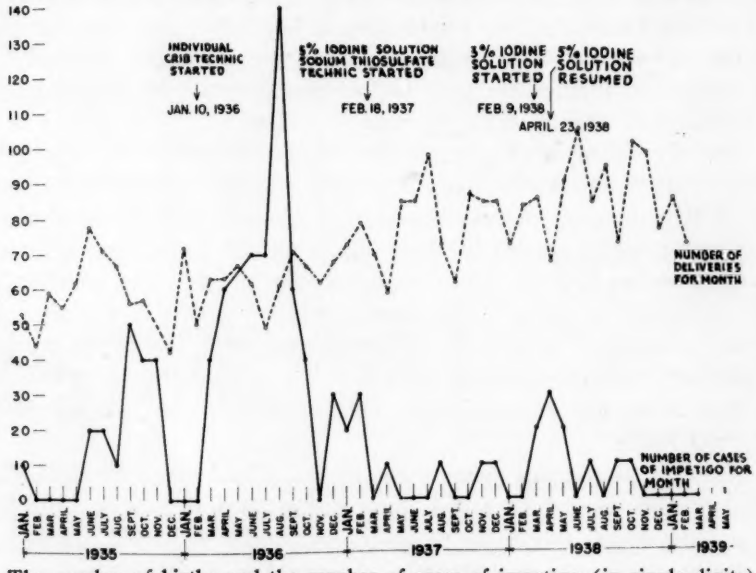
When the accompanying table is examined it will be apparent that simple washing of the hands with soap and hot water, although continued for two minutes, was ineffective. Further, the surface film on the hands produced by the water, soft soap and alcohol was not as sterile as previously believed, and the underlying surface was moderately infectious after it had been thoroughly scrubbed. Finally, the hands treated with compound solution of iodine U. S. P. had a minimum of infection both after soaking and after scrubbing. While the hands were not sterile, they apparently were clean enough to prevent the spread of impetigo, as our clinical experience bears out.

The accompanying chart will demonstrate our clinical success with this procedure. Strict individual crib technic was not sufficient to check the outbreaks, as there was a severe epidemic after its initation. We had a mild reoccurrence in September and October when we endeavored

to reduce the concentration of the iodine solution to 3 per cent; but we have had no more outbreaks after returning to the 5 per cent solution.

The advantages of this procedure are that it is practical, it is apparently effective, it is not detrimental to the nurses' hands and it is inexpensive. The cost of making a liter of the iodine solution and of the sodium thiosulfate is approximately 14½ cents. We advocate changing the solution every eight hours.

The disadvantage of the technic is that the iodine solution is highly volatile in 5 per cent solution, which is one of the reasons we tried to reduce the concentration to 3 per cent. The walls and ceilings become moderately discolored, and any exposed metal, including stainless steel and chromium (except monel metal), becomes tarnished. For this



The number of births and the number of cases of impetigo (in single digits) in the nursery of St. Mary's Hospital in relation to the kind of care taken to prevent the spreading of impetigo.

reason we enameled all exposed surfaces, except the individual crib and service tables, which were of monel metal. The terrazzo floors are corroded by the iodine solution, but this damage was minimized by keeping heavy linoleum, which is impervious to iodine, under the basins.

The more we use this technic the better we like it. It has simplified nursery procedure. No longer do we repaint cribs and nursery walls when we have a sporadic case of impetigo, which, incidentally, we believe to be of maternal origin. The infant is moved from the nursery, the crib and bedding are sterilized and the nursery procedure goes on as usual, except that for the next week the solutions are changed every six hours.

490 Post Street.

ASSIMILATION OF PROTEIN BY YOUNG CHILDREN WITH THE NEPHROTIC SYNDROME

II. EFFECT OF DIETARY FAT AND CARBOHYDRATE ON NITROGEN BALANCE

LEE E. FARR, M.D.
NEW YORK

During previous studies [1] on the effects of a varying intake of protein on assimilation of nitrogen by children with the nephrotic syndrome, it was noted in a preliminary study period that apparently more nitrogen was assimilated with a high fat than with a low fat diet, the nitrogen intake remaining constant. Rubner [2a] performed experiments indicating that with a constant intake of protein assimilation of nitrogen is promoted by an increase in the fat content of the diet, with an accompanying increase of total calories. Voit [2b] showed that during starvation the rate of protein metabolism depends on the amount of fat in the body; with the disappearance of stored fat destruction of protein proceeds at an accelerating pace. In the dog fed meat washed for removal of easily extractable nitrogen, nitrogen equilibrium was established when the nitrogen intake was three and a half times the nitrogen loss during starvation (Voit and Korkunoff [2c]). By addition of fat to the diet this proportion was reduced to about one and a half (Voit and Korkunoff [2d]). It seemed possible that such a mechanism might be operative in these children. Previous studies by Page and me [3] on lipid metabolism of similar patients had revealed that high fat diets resulted in no adverse effects and that changes in the total amount of dietary fat consumed produced no consistent effect on lipemia.

MATERIAL AND METHODS

Both patients were boys, J. M. 6 years and J. C. 4½ years old. J. M. had been observed in the Hospital and the Clinic of the Rockefeller Institute for three years; J. C. had been a patient in this hospital for the preceding seven months. Throughout the period of observation for this study the patients were kept on

From the Hospital of the Rockefeller Institute for Medical Research.

1. Farr, L. E.: The Assimilation of Protein by Young Children with the Nephrotic Syndrome, Am. J. M. Sc. **195**:70 (Jan.) 1938.

2. Cited by Lusk, G.: The Elements of the Science of Nutrition, ed. 4, Philadelphia, W. B. Saunders Company, 1928, (*a*) p. 315; (*b*) p. 107; (*c*) p. 187; (*d*) p. 315.

3. Page, I. H., and Farr, L. E.: The Influence of High and Low Fat Diets and Thyroid Substance on Plasma Lipids of Nephrotic Patients, J. Clin. Investigation **15**:181 (March) 1936.

weighed isocaloric diets, individually prepared in the diet kitchen of the hospital under the supervision of Miss G. Drew. J. M. received 1,200 calories per day and J. C. 1,100 calories. The sodium chloride content of the diets was kept low, never exceeding 1 Gm. per day. The protein content of the diets was fixed at 3 Gm. of protein per kilogram of ideal body weight (accepted average weight for height and age) per day. This level, as I have shown,[1] is compatible with maximum assimilation of nitrogen. The children were given this amount of protein for several weeks prior to this study to make certain that they were in nitrogenous equilibrium. During the first test period the fat in the diet was reduced to 1 Gm. per kilogram of ideal body weight per day, and the carbohydrate was increased to keep the caloric intake constant. After seven days had been allowed for equilibrium to be established, a three-day test period was maintained, total urine and stool collections being kept separate. The stools were marked at the beginning and end of each period by feeding carmine. The diet was then changed to include, successively, 2, 3, 4, 5 and 2 Gm. of fat per kilogram of ideal body weight, with reciprocal changes in the carbohydrate content to maintain the same total number of calories in the diet. In each instance seven days were allowed for equilibrium before the three-day test. In addition to the regular diet 5 Gm. of fresh brewers' yeast and two capsules of halibut liver oil were given daily. Measured fluids were given ad libitum throughout the period of observation. The children took all the diets well, were free from clinical evidences of infection, and were almost completely afebrile throughout the period of study, J. C. having a temperature running above 99.6 F. on only two days, not during a test period, when it rose to 100. J. M. had a temperature ranging from 99.6 to 100 F. on the first test day of period 6, but otherwise was afebrile. All temperatures were taken by rectum. The children were permitted such activity as their physical condition would allow. There was no nausea, vomiting, diarrhea or constipation at any time during the period of observation. During the first period J. C. had a sudoriferous rash and during the fifth period papular vesicular urticaria. There had been no change in diet to account for this, and there were no constitutional symptoms. The entire study of both children was carried on during July and August.

Analyses.—The total urinary nitrogen was determined gasometrically by the micro-Kjeldahl method of Van Slyke.[4] Urinary nonprotein nitrogen was estimated in the same manner on trichloracetic acid filtrates. The difference was calculated as urinary protein nitrogen. Fecal nitrogen also was determined by the micro-Kjeldahl method of Van Slyke, the stools being treated with concentrated sulfuric acid as soon as they were obtained; this acid fecal mixture was then made up to a known volume, and aliquots were removed for analysis. Analyses of fecal nitrogen were made in triplicate: all other analyses were made in duplicate. The composition of the diet was calculated from tables used in the diet kitchen which were compiled from standard works on food values. Previous control analyses of diets agreed well with calculated values.

RESULTS

The data are summarized in the table and in the chart.

For neither patient was any effect of the interchange of fat and carbohydrate evident in the nitrogen balances. J. M. had a positive

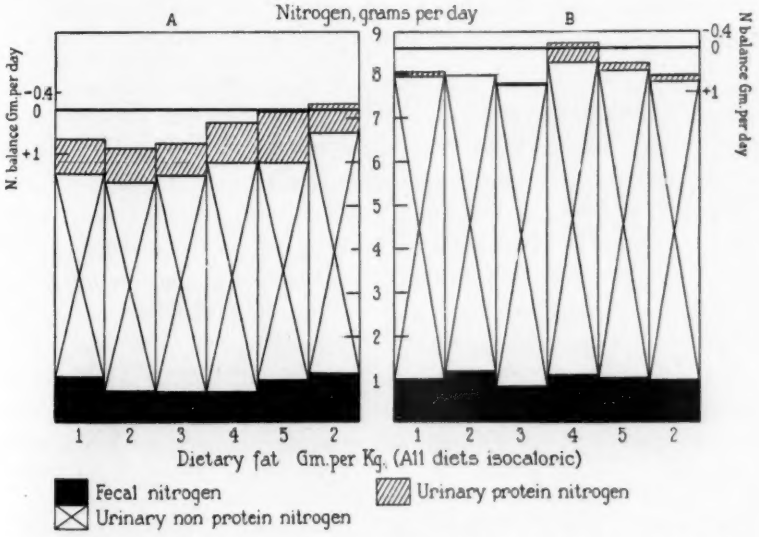
4. Van Slyke, D. D.: Gasometric Micro-Kjeldahl Determination of Nitrogen, J. Biol. Chem. **71**:235 (Jan.) 1927.

Effect of Dietary Fat on Nitrogen Balance

Patient	Period	Daily Diet: Fat, Gm. per Kg.	Daily Diet: Carbohydrate, Gm. per Kg.	Daily Diet: Protein, Gm. per Kg.	Daily Average Nitrogen Balance: Total Nitrogen Fed *a* Gm.	Total Urinary Nitrogen *b* Gm.	Total Urinary Nonprotein Nitrogen *c* Gm.	Total Fecal Nitrogen *d* Gm.	Nitrogen Balance $a-(b+d)$ Gm.
J. M.*	1	1	11	3	8.650	7.000	6.983	1.034	0.616
	2	2	9	3	8.650	6.747	6.747	1.197	0.706
	3	3	7	3	8.650	6.989	6.983	0.838	0.823
	4	4	4.5	3	8.650	7.609	7.167	1.117	−0.076
	5	5	2.5	3	8.650	7.218	7.046	1.046	0.386
	6	2	9	3	8.650	6.960	6.857	0.974	0.716
J. C.†	1	1	13	3	7.200	5.453	4.633	1.098	0.649
	2	2	11	3	7.200	5.597	4.800	0.771	0.832
	3	3	8.5	3	7.200	5.675	4.913	0.756	0.769
	4	4	6	3	7.200	6.099	5.211	0.720	0.381
	5	5	4	3	7.200	6.177	4.987	0.999	0.024
	6	2	11	3	7.200	6.142	5.500	1.180	−0.122

* Calories per kilogram of ideal weight per day, 67; ideal weight 18 Kg., actual weight 19.5 Kg.

† Calories per kilogram of ideal weight per day, 73; ideal weight 15 Kg., actual weight 16 Kg.



Graphic representation of data. *A*, chart of J. C. (at the age of 4½ years, ideal weight 15 Kg., actual weight 16 Kg.) and *B*, chart of J. M. (at the age of 6 years, ideal weight 18 Kg., actual weight 19.5 Kg.). There is seen no consistent effect of varying intake of fat on assimilation of nitrogen. The irregular assimilation of J. M. and the variation of J. C. are characteristically associated with the nephrotic syndrome except during actual recovery.

nitrogen balance in every period except period 6, when the balance was slightly negative because of a marked increase in the excretion of nonprotein nitrogen. Clinically he was free of infection or other constitutional disturbance at this time, although on the first day of this test period he had an elevation of temperature to 100 F. J. C. had a positive nitrogen balance in every period except 6. He also showed no constitutional disturbances at this time except for one day, the first of the period, when his rectal temperature ranged from 99.5 to 100 F. The apparent trend toward a negative nitrogen balance in J. C. during the first five periods does not appear to be due to the dietary changes, as during period 6, when the diet was changed to its original content, the nitrogen balance became negative. Rough analyses for fecal fat with a wet extraction method indicated that all of the dietary fat was absorbed.

It appears that some factor other than the fat and carbohydrate content of the diet was responsible for the single period of negative nitrogen balance observed for each patient.

CONCLUSION

The nitrogen balance of 2 young children with the nephrotic syndrome given a fixed allowance of nitrogen was unaltered by change in the quantity of fat and carbohydrate consumed in isocaloric diets.

ASSIMILATION OF PROTEIN BY YOUNG CHILDREN WITH THE NEPHROTIC SYNDROME

III. EFFECT OF NEPHROTIC CRISES ON ASSIMILATION OF NITROGEN

LEE E. FARR, M.D.
NEW YORK

Previous observations of the effect of dietary protein,[1] fat and carbohydrate [2] on the nitrogen balance of young children with the nephrotic syndrome revealed the fact that protein intakes above the optimum of 3 Gm. daily per kilogram of body weight tended to produce a less positive or even a negative nitrogen balance in these children. There still remained unexplained fluctuations in the nitrogen balance unrelated to diet and in the absence of infection.

It is well known that nephrotic children are susceptible to acute infections, particularly pneumococcic peritonitis. MacLeod and Farr [3] found that these attacks are usually due to infection not by freshly acquired organisms but by organisms which have been carried for some time. The infections appear to result primarily from some metabolic disturbance, as a result of which resistance is lowered and a previously harmless organism invades the blood and the peritoneal fluid.

Since publication of the report just cited [3] we have found that the acute metabolic disturbance can occur without being followed by the infection. There are fever, abdominal pain, prostration and acute malaise, without demonstrable organisms in the blood or in the peritoneal fluid. Without infection, the attack passes in twelve to forty-eight hours. The present paper deals with the nitrogen balance during these noninfectious attacks, which will be termed "nephrotic crises."

For comparison, I also include studies made before, during and after acute infections of the respiratory tract without nephrotic crises.

From the Hospital of the Rockefeller Institute for Medical Research.

1. Farr, L. E.: The Assimilation of Protein by Young Children with the Nephrotic Syndrome, Am. J. M. Sc. **195**:70 (Jan.) 1938.

2. Farr, L. E.: Assimilation of Protein by Young Children with the Nephrotic Syndrome: II. Effect of Dietary Fat and Carbohydrate on Nitrogen Balance, Am. J. Dis. Child., this issue, p. 935.

3. MacLeod, C. M., and Farr, L. E.: Relation of the Carrier State to Pneumococcal Peritonitis in Young Children with the Nephrotic Syndrome, Proc. Soc. Exper. Biol. & Med. **37**:556 (Dec.) 1937.

MATERIAL AND METHODS

Both patients were boys, J. T. 7 years and J. C. 5½ years old. They had been observed in the Hospital and the Clinic of the Rockefeller Institute for Medical Research for three years and one and one-half years respectively. Both had a history of insidious onset of edema without antecedent infection.

The attack of nephrosis observed in J. T. in the study presented here was a recurrence which began six months before the commencement of the study. During the preceding seventeen months, spent partly in this hospital and partly at home, he appeared to be well according to all the criteria applied; that is, his plasma proteins were normal, the urea clearance and maximum nonprotein specific gravity of the urine were normal, he was able to excrete over 10 Gm. of salt a day, urinary sediment was normal and there was no proteinuria. He was admitted to the hospital six months before the start of these observations, with low plasma proteins, proteinuria, edema and retention of salt. He had been receiving a weighed low salt diet containing 2 Gm. of protein per kilogram of ideal body weight since admission, with no improvement in his condition up to the time these studies were begun. He tended to have an irregular low grade fever throughout the period; that is, on the average, about one day of three his rectal temperature would rise from 98 to 100.5 F. These elevations usually occurred in the afternoon and were thought to be due in part to his activity. Except in period 8, as will be noted, he was free from all clinical evidences of infection. Further data are shown in chart 1.

J. C. had been on a weighed diet for fifteen months prior to commencement of this study. Renal function had improved, as measured by the urea clearance, but there had been no change in plasma protein or proteinuria for twelve months previously. The temperature curve was flat, the rectal temperature usually varying between 98 and 99.6 F., except in period 4, when it spurted sharply to 104 and remained elevated for about thirty hours, dropping by crisis after that period. Subsequently the temperature curve was flat. In period 10 there was a similar sharp elevation to 102 F., the level returning to normal within twenty-four hours, and again in period 11, with an elevation to 103 F. Each of these bouts of fever was accompanied by extreme malaise, sharp abdominal pain, sometimes localized, intense pallor of the skin and at times hyperesthesia of the skin over the lumbar region, the abdomen, or the inner aspects of the thighs. There was some resistance of the abdominal wall to palpation, but at no time was the rigidity involuntary. In some attacks there was localized abdominal tenderness to palpation. In every instance, abdominal paracentesis was performed and sufficient fluid was withdrawn for culture and microscopic study. Repeated blood cultures made during the febrile period were all negative during this study. Physical examination of the nose and throat, chest and extremities gave uniformly negative results. The entire episode conformed to the clinical syndrome which in this paper is termed nephrotic crisis. Frequently pneumococcic peritonitis and bacteremia developed during the crises, and this patient has survived five culturally proved attacks of pneumococcic peritonitis, one occurring before admission to the hospital. The diagnosis of peritonitis does not seem to be warranted unless organisms are demonstrated in the ascitic fluid. The relation of these crises to the progress of nephrosis cannot be discussed at this time, but it seems likely they may be the result of some underlying metabolic difficulty and are not chance intercurrent infection. Further clinical data are shown in chart 2.

Throughout the period of study both patients were given weighed diets prepared in the diet kitchen of the hospital under the supervision of Miss M. Rhine. The protein intake was 2 Gm. per kilogram of ideal body weight throughout,

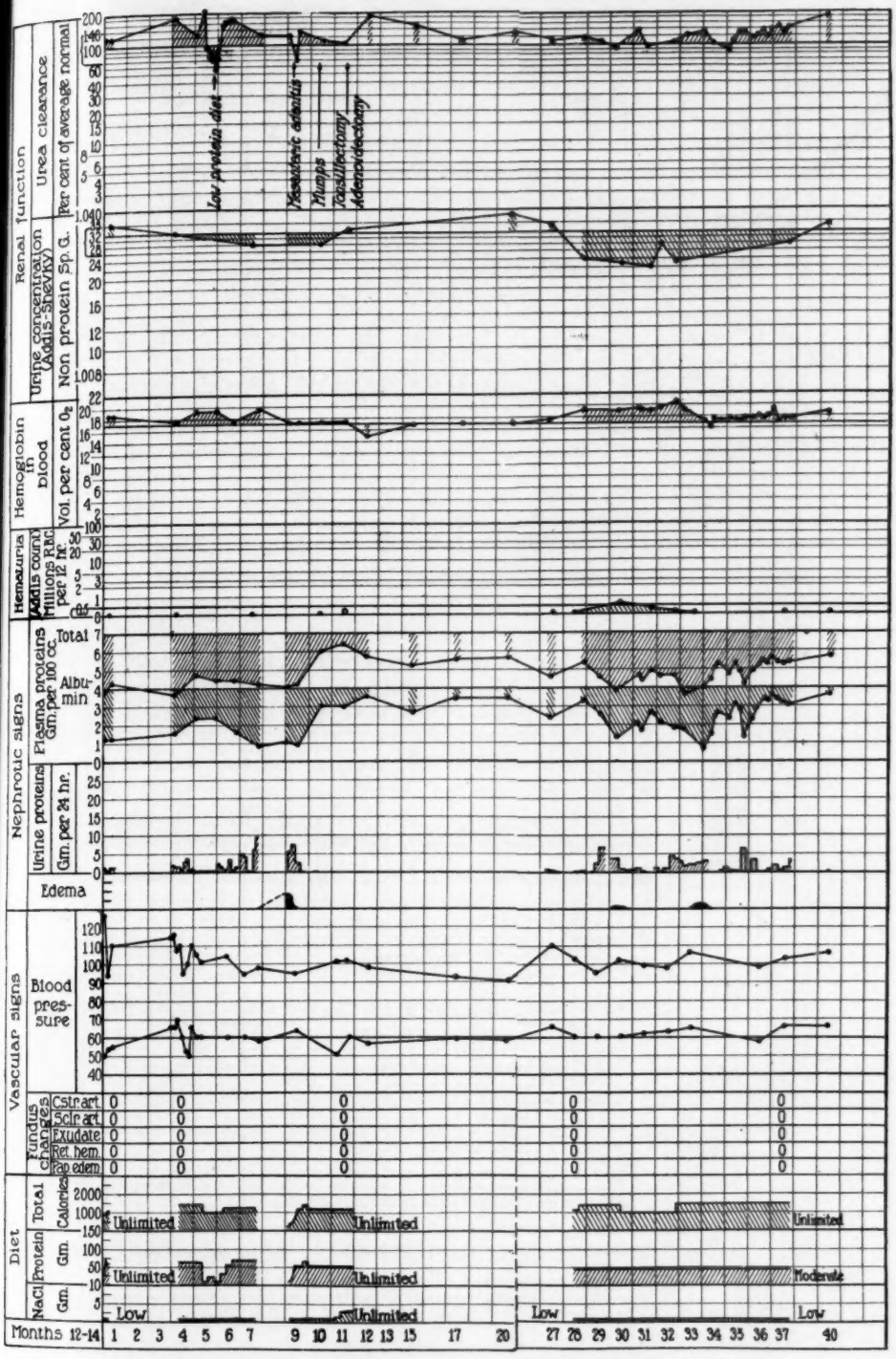


Chart 1.—Data summarizing laboratory and clinical observations on J. T. during both attacks of nephrosis. The study presented in this paper was carried on during months 34 to 37, inclusive. The last months show the rise of albumin and cessation of proteinuria characteristic of recovery from nephrosis. The urea clearance is still abnormally high, being one of the last nephrotic signs to disappear. At the age of 4 years the height was 106 cm. and the ideal weight 17.5 Kg. At 6 years the height was 122.5 cm. and the ideal weight 24 Kg.

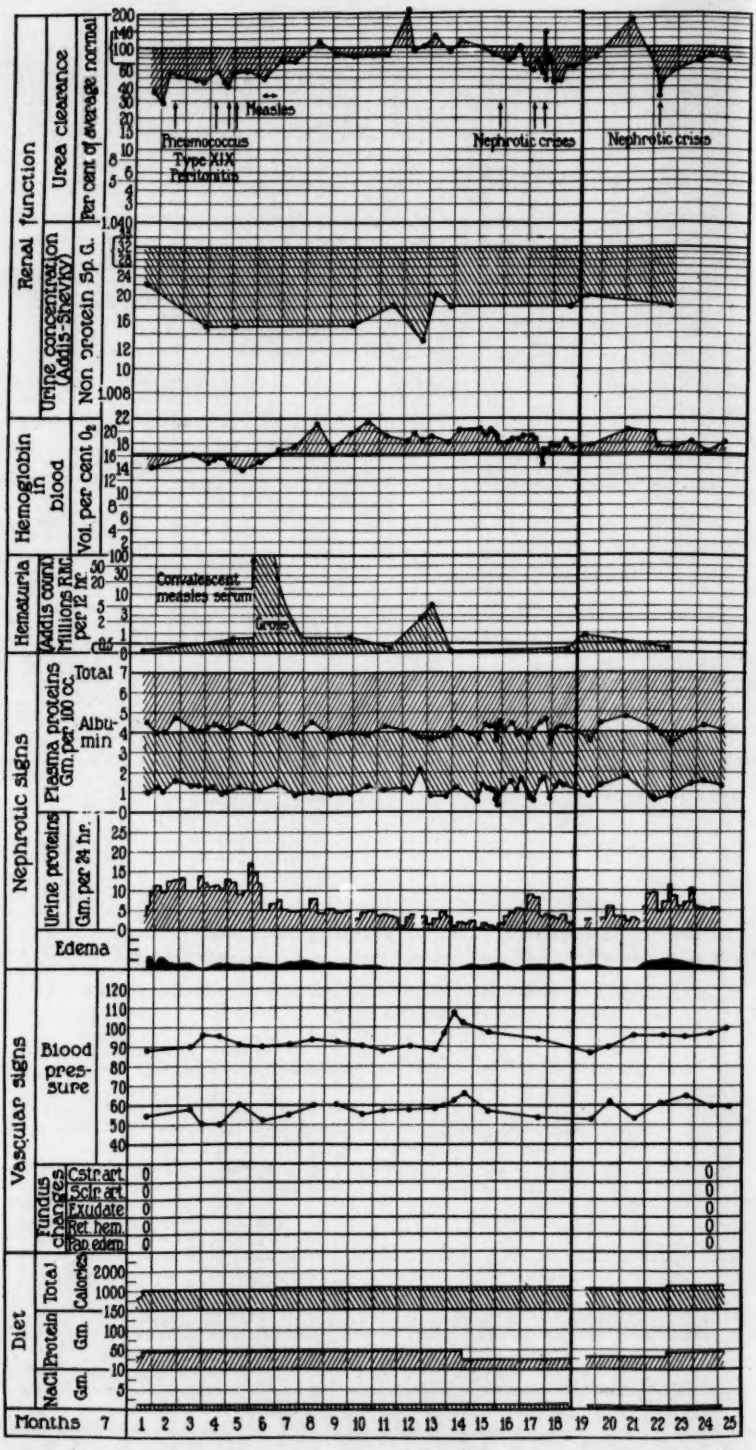


Chart 2.—Data summarizing laboratory and clinical observations on J. C. during hospitalization. The study presented in this paper was carried on during months 15 to 19. The persistent hypoproteinemia and proteinuria indicate lack of any tendency to recover. The low urinary specific gravity and frequently subnormal urea clearance indicate that excretory function also was definitely affected. The condition was apparently chronic, but recovery may yet occur. At the age of 4 years the height was 98 cm. and the ideal weight 15 Kg. At 6 years the height was 100.5 cm. and the ideal weight 15.9 Kg.

and the fat and the carbohydrate content of each diet were also constant. The patients received 5 Gm. of fresh brewers' yeast and 2 capsules of halibut liver oil daily in addition to their regular diet. Measured fluids were allowed ad libitum. The patients were allowed to get out of bed and play in the room during the day, when their condition permitted. It is noteworthy that throughout the period of study there were no refusals of food or vomiting. Much credit for this is due to the cooperation of Miss E. Glantz and the nurses under her as well as to the careful planning and cooking of varied diets by the staff of the diet kitchen. The total period of observation was divided into sixteen weeks. At the beginning of each week blood was taken for chemical analysis and test of renal function, and carmine was given to mark the stools. Constipation was avoided by administration of adequate amounts of fluids at all times.

Analyses.—Specimens of urine were kept free from bacterial contamination, as the patients voided directly into sterile bottles, which were tightly stoppered and placed in the ice box at the end of each twelve hour period. At the end of a week the specimens were measured and mixed in a suitable container, and an aliquot was removed for analysis. It has been possible to keep urine for several months in this way without apparent bacterial contamination. The total urinary nitrogen was determined by the gasometric method of Van Slyke.[4] Urinary nonprotein nitrogen was estimated in the same manner with urinary filtrates after deproteinization with trichloracetic acid. The difference was calculated as protein nitrogen. Fecal nitrogen was also estimated by the Van Slyke gasometric method. The stools were treated with concentrated sulfuric acid as soon as they were obtained, the total acid fecal mixture was made up to a known volume at the end of a week, and aliquots were removed for analysis. Estimations of fecal nitrogen were made in triplicate; all other analyses were made in duplicate. The composition of the diet was calculated from tables used in the diet kitchen. These were calculated from standard works on food values and agreed well with actual determinations.

RESULTS

The results are summarized in table 1 and in charts 3 and 4.

Nitrogen Balance.—The observed nitrogen balances in these 2 patients differed widely. J. T. had a positive nitrogen balance for fifteen of the sixteen weeks of the test. The single period during which he had a negative nitrogen balance was associated with development of a mild infection of the upper respiratory tract. Signs of infection were limited to a low grade fever and coryza. He had apparently recovered by the end of the week. After recovery, his nitrogen balance again became positive and remained so until the study was ended. It seems likely that the pattern of nitrogen balance noted for this patient is that usually followed by a nephrotic child during the period of recovery. It is interesting that the increase in urinary nonprotein nitrogen and proteinuria during the week of illness was out of all proportion to the apparent severity of the illness, thus demonstrating with considerable vigor the ease with which the replacement of tissue and blood proteins

4. Van Slyke, D. D.: Gasometric Micro-Kjeldahl Determination of Nitrogen, J. Biol. Chem. **71**:235 (Jan.) 1927.

can be interfered with in these patients. The fecal nitrogen remained constant throughout the study, as would be expected in the absence of gastrointestinal upsets. Thus the loss of nitrogen in period 8 was caused by an increase of both nonprotein nitrogen and protein in the urine. It seems likely that the increase of urinary nonprotein nitrogen was largely due to destruction of tissue. The excess of nitrogen assimilated during the first four weeks, as compared with the last five weeks, seems due to more rapid replacement of tissue during the early phase of recovery. Lusk [5] cited Rubner's experiment which showed that with a constant

Assimilation of Nitrogen by Two Boys with the Nephrotic Syndrome

Patient and Age, Yr.	Period	Total Nitrogen Fed *a*, Gm.	Total Urinary Nitrogen *b*, Gm.	Total Urinary Nonprotein Nitrogen *c*, Gm.	Total Fecal Nitrogen *d*, Gm.	Nitrogen Balance *a*—(*b*+*d*) Gm.
J. T., 7	1	7.680	5.538	5.042	0.754	1.388
	2	7.680	5.036	5.036	0.982	1.662
	3	7.680	5.152	5.152	0.982	1.546
	4	7.680	5.612	5.518	0.921	1.147
	5	7.680	6.017	5.777	1.066	0.597
	6	7.680	5.449	5.365	0.936	1.295
	7	7.680	5.320	5.279	1.094	1.266
	8	7.680	7.194	6.177	0.974	—0.488
	9	7.680	6.137	6.008	0.962	0.581
	10	7.680	6.240	5.765	0.994	0.446
	11	7.680	5.335	5.264	0.886	1.459
	12	7.680	6.061	6.053	0.987	0.632
	13	7.680	6.147	5.990	1.115	0.418
	14	7.680	6.256	5.948	1.076	0.348
	15	7.680	6.086	5.995	1.076	0.518
	16	7.680	6.330	6.085	1.044	0.306
J. C., 5½	1	5.120	3.545	3.334	0.717	0.858
	2	5.120	4.210	3.918	0.905	—0.005
	3	5.120	4.391	4.157	0.905	—0.176
	4	5.120	4.367	4.247	0.921	—0.168
	5	5.120	4.240	3.944	0.810	0.070
	6	5.120	4.434	3.898	0.951	—0.265
	7	5.120	4.479	3.743	1.100	—0.459
	8	5.120	4.182	3.329	1.043	—0.105
	9	5.120	4.260	3.433	1.116	—0.156
	10	5.120	4.824	3.489	1.084	—0.786
	11	5.120	4.680	3.440	0.710	—0.270
	12	5.120	3.709	3.186	0.923	0.488
	13	5.120	4.417	3.773	0.867	—0.164
	14	5.120	3.471	2.906	0.974	0.675
	15	5.120	3.631	3.087	0.858	0.631
	16	5.120	4.066	3.451	0.869	0.185

nitrogen intake a dog will assimilate more nitrogen when in a state of nitrogen depletion than he will retain as he approaches optimal nutritive conditions. He also cited [6] McCollum's experiment on a hog showing the same phenomenon.

The state of nitrogen balance of J. C. was markedly different. Throughout the study he was in a phase of active nephrosis, and his balance was negative for ten of the sixteen weeks. For the sixteen weeks as a whole he had, however, a slightly positive balance. It seems

5. Lusk, G.: The Elements of the Science of Nutrition, ed. 4, Philadelphia. W. B. Saunders Company, 1928, p. 372.

6. Lusk,[5] p. 327.

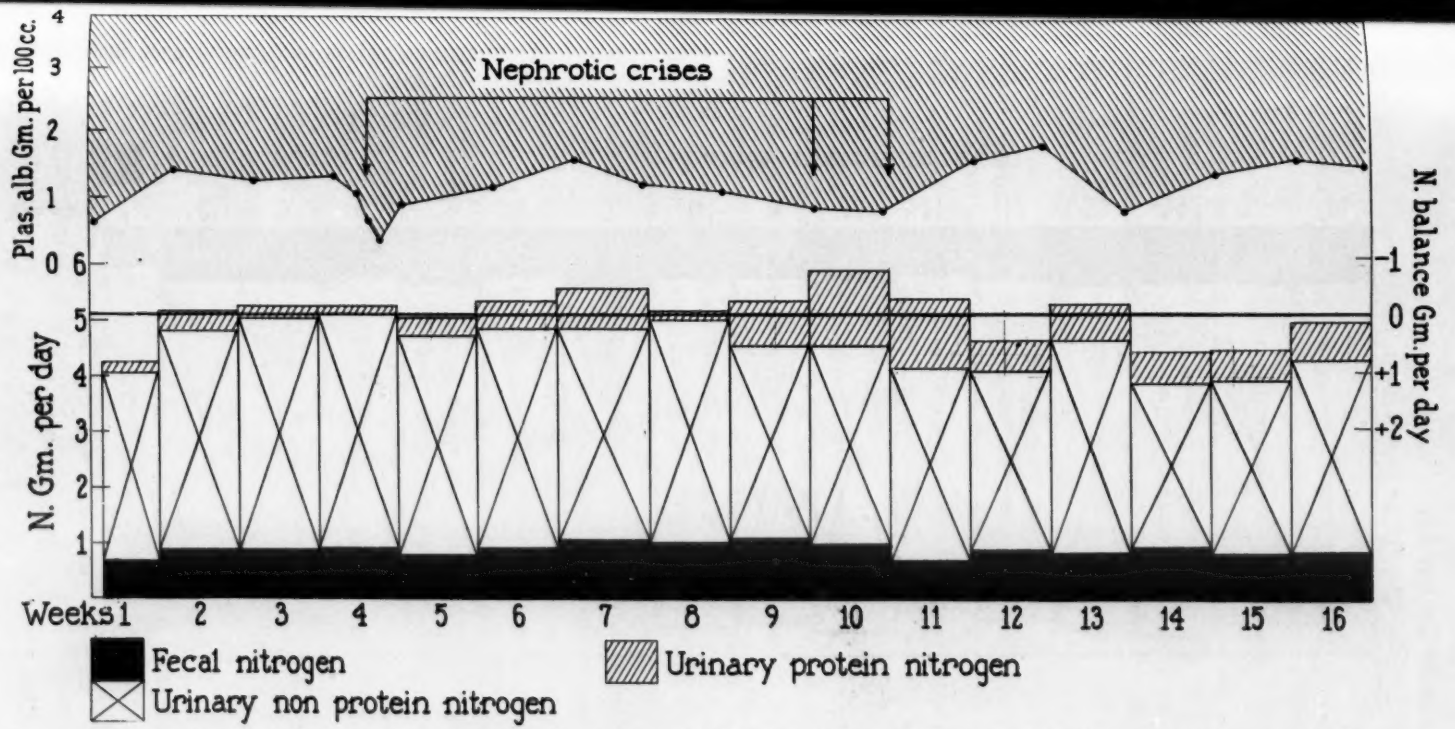


Chart 3.—The relation of the nitrogen balance to nephrotic crises. The patient, J. C., had three noninfectious nephrotic crises, indicated by arrows. The results indicate that, unlike acute infections, the noninfectious crises can occur without a marked increase in loss of nitrogen. Contrast this chart with chart 4. The characteristic sharp depression of the plasma albumin level is shown for only one nephrotic crisis. Note the variability in assimilation of nitrogen. At the age of 5½ years the ideal weight was 16 Kg. and the actual weight 17 Kg. The dietary intake of nitrogen was 5.120 Gm. daily, equivalent to 2 Gm. of protein per kilogram of ideal body weight.

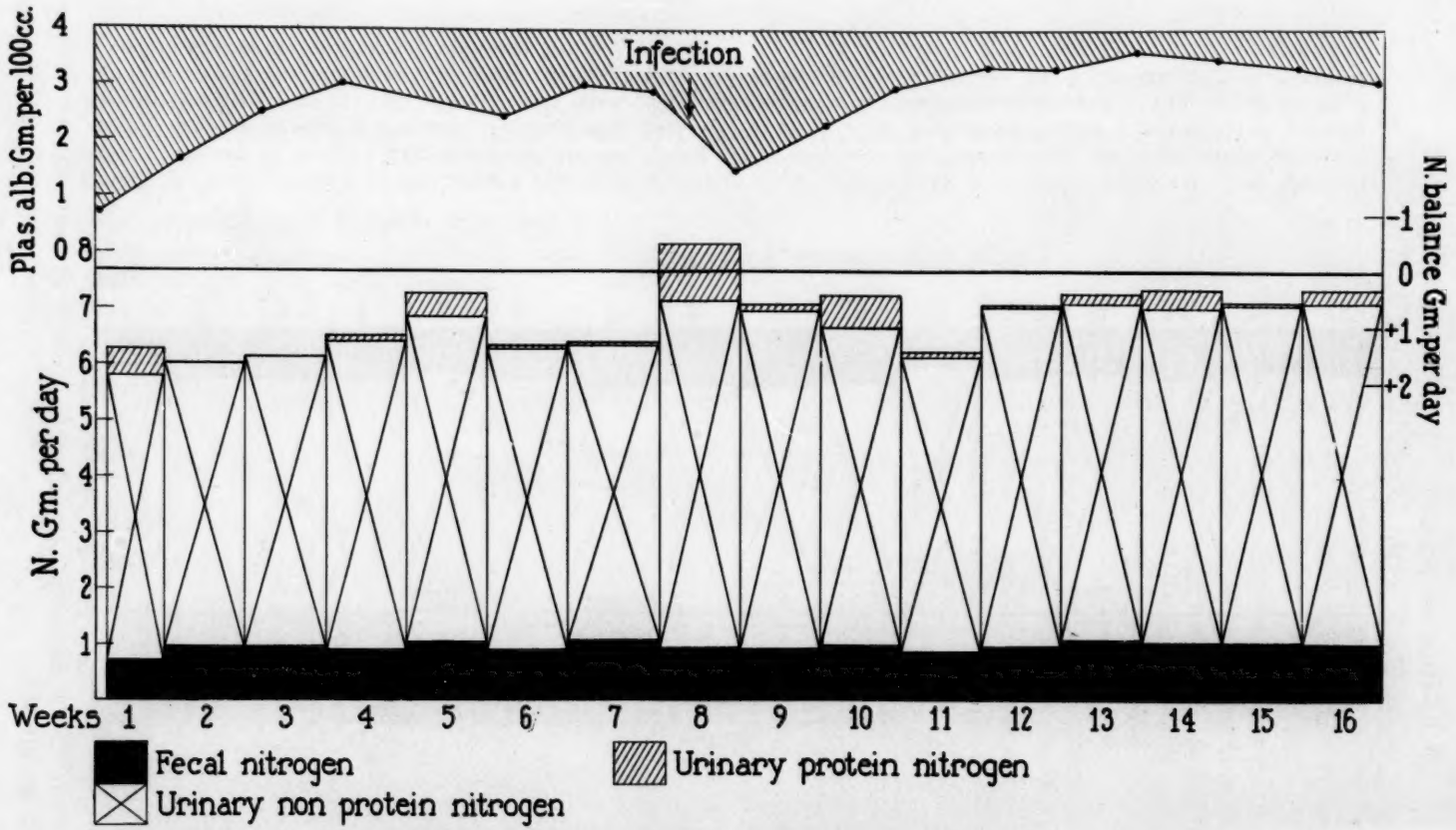


Chart 4.—The nitrogen balance of J. T. while he was recovering from nephrosis, showing the uniform pattern interrupted only by a marked increase in loss of nitrogen during acute infection in period 8. At the age of 7 years the ideal weight was 24 Kg. and the actual weight 21 Kg. The dietary intake of nitrogen was 7.680 Gm. daily, equivalent to 2 Gm. of protein per kilogram of ideal body weight.

that this condition must prevail during the phases of nephrosis in which the patient is showing no tendency to recover. The patient's loss of nitrogen seemed to be a result of at least two factors: proteinuria and excessive excretion of urinary nonprotein nitrogen. During the first few weeks of the study proteinuria was at a minimum, and the negative nitrogen balance was largely due to a sharp increase in the excretion of urinary nonprotein nitrogen. During the last half of the study the loss of nitrogen as urinary protein became significant, and the balance was a resultant of these two factors. There was no direct evidence indicating whether the large percentage of nitrogen excreted as nonprotein nitrogen in the urine during the first half of the study was due to breakdown of tissue or to failure of the patient to synthesize protein from the nitrogen ingested, with degradation of the amino acids to urea. It should be noted that the nitrogen balance was negative for two weeks prior to the first nephrotic crisis in period 4 and also prior to the two succeeding crises, in periods 10 and 11. Fever alone did not increase the loss of nitrogen.

Proteinuria.—J. T. showed marked variations in proteinuria during the period of observation. For two of the sixteen weeks (2 and 3) no protein was detectable in the urine, while during the remaining fourteen weeks the daily loss of protein varied from 0.05 to 6.36 Gm. per day. Excluding period 8, during which there was an infection of the upper respiratory tract, the maximum protein content of the urine was 3.53 Gm. per day. This variation in proteinuria had not been uncommon in our patients when factors of recovery seemed to be in the ascendancy. The absence of protein in the urine was not always associated with recovery. One patient followed in this clinic for five years has seldom lost more than 0.1 Gm. of protein per day for the past four years, yet there has been no apparent metabolic improvement in his nephrosis; the plasma albumin level remains fixed at about 1.3 Gm. per hundred cubic centimeters, although when it is above the critical edema level [7] he is free from edema and normal in appearance.

The amount of protein lost by J. C. was somewhat more constant. During his first nephrotic crisis (period 4) the protein content of the urine decreased from about 1.56 to 0.75 Gm. per day, while during the second attack (period 10), which was mild, there was an increase to the maximum observed in this study, 8.33 Gm. per day. During the third nephrotic crisis (period 11) the protein output remained high, being 7.74 Gm. per day, but was lower than in the immediately preceding crisis. There was no certain relation between the apparent severity of the crises and the degree of proteinuria, although during the first episode, which was most severe, the proteinuria was least, and during

7. Farr, L. E., and Van Slyke, D. D.: Relation Between Plasma Protein Level and Edema in Nephrotic Children, Am. J. Dis. Child. **57**:306 (Feb.) 1939.

the second episode, which was mildest, it was greatest. Since the nitrogen balance was negative during each of these periods, it appears that the crises are connected with either a failure to synthesize protein or an extremely rapid destruction of protein, so that the quantity available for excretion may in some instances be sharply reduced. There is no evidence at this time which conclusively points to either factor, but it seems that failure of synthesis is the more probable cause.

Plasma Albumin.—In both cases the level of the plasma albumin seemed to be more closely related to fluctuations in the urinary excretion of nonprotein nitrogen than to the degree of proteinuria. Although loss of protein in the urine must play some role in the reduction of the level of the plasma albumin, it appears that in these children the assimilation of dietary protein, as measured by the difference between the nitrogen fed and that excreted in the urine as nonprotein nitrogen, was a more sensitive indicator of the protein metabolism (charts). Increased excretion of nitrogen may be due either to failure to synthesize protein, during deficit of plasma amino acids, or to rapid destruction of already formed protein or to a combination of the two. The combination seems most likely during the nephrotic crises, as exemplified by period 4 for J. C. The marked reduction of plasma albumin noted during the episode is constant for all nephrotic children during such episodes, and I have observed it many times. It seems reasonably certain that the same phenomenon would have been evident during the crises in periods 10 and 11 had daily determinations of plasma albumin been made, as I have observed it in every child followed in sufficient detail. Restoration of the plasma albumin from these exceedingly low levels to the precrisis level is rapid, occurring within a few days. It is not assisted by transfusion. Since the plasma globulin and, initially, the hemoglobin tend to remain fairly constant, it seems reasonably certain that the reduction in plasma albumin is real and not due to a change in blood volume.

SUMMARY AND CONCLUSIONS

The nitrogen balances of 2 young children with the nephrotic syndrome given a fixed diet showed marked spontaneous changes which preceded clinical evidence of changes in the severity of the syndrome.

Mild infections of the upper respiratory tract tend to produce a negative nitrogen balance. This is caused by failure to assimilate dietary protein and by increase in proteinuria.

Nephrotic crises, when unaccompanied by pneumococcic bacteremia and peritonitis, apparently are a reflection of a preexisting negative nitrogen balance and are not uniformly accompanied by an increase in nitrogen loss or necessarily by an increase of proteinuria. Such episodes appear to be an accurate reflection of an acute disturbance of protein nutrition in a patient already manifesting marked evidences of inability to assimilate nitrogen.

RATE OF APPEARANCE OF OSSIFICATION CENTERS FROM BIRTH TO THE AGE OF FIVE YEARS

L. W. SONTAG, M.D.

DOROTHY SNELL, M.D.
AND
MARGARET ANDERSON, B.A.
YELLOW SPRINGS, OHIO

Roentgenologists, pediatricians and persons engaged entirely in research on child development have proposed numerous methods for appraising the skeletal changes of children. These methods have been devised in general to provide standards of osseous development. The roentgenologist and the pediatrician have used them to determine whether individual children were skeletally advanced or retarded, since appraisal of advancement or retardation is an aid in the diagnosis of endocrine [1] and nutritional [2] disorders. Research workers in the field have been interested because they wished an objective measure of the progress of one of the developing systems of the child for comparison with the progress of other developing systems, for correlation with his mental scores,[3] economic status, height, weight [4] or dentition.[5] Out of

---

From the Samuel S. Fels Research Institute, Antioch College.

1. (*a*) Engelbach, W.: Endocrine Medicine, Springfield, Ill., Charles C. Thomas, Publisher, 1932, vol. 2, pp. 49-56. (*b*) Clark, D. M.: Practical Value of Roentgenography of the Epiphyses in the Diagnosis of Pre-Adult Endocrine Disorders, Am. J. Roentgenol. **35**:752 (June) 1936.

2. Growth and Development of the Child: II. Anatomy and Physiology, White House Conference on Child Health and Protection, New York, Century Company, 1933, p. 28.

3. (*a*) Prescott, D. A.: The Determination of Anatomic Age in School Children and Its Relation to Mental Development, Harvard Monographs in Education, series 1, no. 5, Cambridge, Mass., Harvard University Press, 1923. (*b*) Flory, C. D.: The Physical Growth of Mentally Deficient Boys, Monograph of the Society for Research in Child Development, National Research Council, 1936, vol. 1, no. 6. (*c*) Abernethy, E. M.: Relationship Between Mental and Physical Growth, Monograph of the Society for Research in Child Development, National Research Council, 1936, vol. 1, no. 7.

4. (*a*) Sawtell, R. O.: Ossification and Growth of Children from One to Eight Years of Age, Am. J. Dis. Child. **37**:61 (Jan.) 1929. (*b*) Baldwin, B. C.; Busby, L. M., and Garside, H. V.: Anatomic Growth of Children, Studies in Child Welfare, Iowa City, University of Iowa, 1930, vol. 4, no. 1. (*c*) Kelly, H. J.: Anatomic Age and Its Relation to Stature, Studies in Child Welfare, Iowa City, University of Iowa, 1937, vol. 12, no. 5.

(Footnotes continued on next page)

these various interests have come a variety of methods of skeletal appraisal. Skeletal development includes, of course, differentiation as well as growth. The bones of the human body, undergo changes in shape and function as well as changes in size. The various methods of skeletal appraisal take into consideration to a greater or lesser degree bone growth as well as differentiation, but there is little agreement as to the relative significance or the degree to which the two factors conform.

One of the early methods of appraisal, which has persisted with variations since, is that of Rotch.[6] His is based on thirteen stages of development and density of the centers of ossification. Bardeen [7] presented a finer scale of differentiation, and Todd,[8] changing the emphasis somewhat, dealt in detail with nine stages of maturation at the diaphysio-epiphysial planes. Still other appraisals of anatomic age have been based on the average time of appearance and hence the number of carpal and epiphysial centers present in the hand [9] and tarsal and epiphysial centers of the foot.[10] Much detailed and painstaking labor has been expended also on the study of carpal area [11] as revealed by roentgenograms of the hand and wrist. Skeletal development has been depicted by means of ratios of bone growth measured from roentgenograms. In this respect may be mentioned the "anatomic index"[3a] (the sum of the diameters of the carpal bones, divided by the width of the wrist), the "radial index"[4a] (the relation between the greatest transverse breadth of the radial diaphysis at its distal extremity to the maximum breadth of its corresponding epiphysis) and the "tibial index" [9c] (similar to the preceding one, using the distal tibial epiphysis and its diaphysis). Recently Kelly [4c] investigated twenty indexes and of them found the index CM (the sum of the greatest diameter of the eight carpal bones and the broadest width of the epiphyses of the radius, ulna and the first four metacarpal bones) divided by WD (the average diameter of the wrist) the most valuable indication of anatomic growth.

---

5. Woodrow, H., and Lowell, F.: Some Data on Anatomic Age and Its Relation to Intelligence, Pedagog. Seminary **29**:1 (March) 1922.

6. Rotch, T. M.: Chronologic and Anatomic Age in Early Life, J. A. M. A. **51**:1197 (Oct. 10) 1908.

7. Bardeen, C. R.: Relation of Ossification to Physiological Development, J. Radiol. **2**:1 (June) 1921.

8. Todd, T. W.: Growth and Development of the Skeleton, in Growth and Development of the Child,[2] p. 56.

9. (*a*) Pryor, J. W.: Ossification of the Epiphyses of the Hand, Bull. Univ. Kentucky **8**:1, 1906. (*b*) Stuart, H. C.: Standards of Physical Development for Reference in Clinical Appraisal: Suggestions for Their Presentation and Use, J. Pediat. **5**:194 (Aug.) 1934. (*c*) Wallis, R. S.: How Children Grow, Studies in Child Welfare, Iowa City, University of Iowa, 1931, vol. 5, no. 1. (*d*) Prescott.[3a] Baldwin and his associates.[4b]

10. Footnote 9 *b* and *c*.

11. Baldwin and his associates.[4b] Woodrow and Lowell.[5]

The most extensive studies of skeletal age judged by the appearance of the hand and wrist have been presented by Flory [12] and Todd.[13] Flory based his qualitative scales evaluating skeletal ages of boys and of girls on the number and appearance of the carpals and the epiphyses of the hand and wrist. The determinators of maturity presented in the Todd "Atlas" depend on the appearance of the diaphyses of the metacarpal bones and radius and at the older age levels also on the contour of the carpal bones.

These systems of skeletal appraisal as well as those we have already described use one part of the body only. Irrespective of their possible merit as methods of appraisal of growth and maturation of the hand, their usefulness in relation to the entire system is predicated on the presumption that as the hand grows, so grows the entire skeleton. Kohler,[14] whose momentous roentgenologic text is almost universally used, said, however:

> The most careful investigations have shown beyond a doubt that people equally advanced in health and characteristics do not develop the various osseous centers in anything like the same order; some nuclei are quicker, others slower in development. . . . Further, one cannot infer the stage of growth of the entire bony framework from the growth of any single part of it. The skeleton of the hand, for instance, can be less ossified in one case than in another, whereas the foot and the elbow bones in the first case may be more highly developed.

Akerlund presented studies which substantiate Kohler's contention that a single part of the skeleton may not be used as a criterion for the growth of the whole skeleton. Engelbach [15] said: "It has been observed that some centers are normal for the age, with retardation in time of appearance and size of epiphyses of other joints."

OUR DATA

We have been collecting data which have enabled us to formulate norms of one phase of this developmental picture which we find useful in skeletal appraisal. For the past seven years we have been taking roentgenograms at regular intervals of all the bones and joints of the left upper and lower extremities of 149 normal children whose growth is being studied at the Samuel S. Fels Research Institute. We are presenting here data and curves of the time of appearance of sixty-seven

12. Flory, C. D.: Osseous Development in the Hand as an Index of Skeletal Development, Monograph of the Society for Research in Child Development, National Research Council, 1936, vol. 1, no. 3.

13. Todd, T. W., and others: Atlas of Skeletal Maturation (Hand), St. Louis, C. V. Mosby Company, 1937.

14. Kohler, A.: Roentgenology, New York, William Wood & Company, 1928, p. 1.

15. Engelbach,[1a] p. 50.

of the centers, both primary and epiphysial, which with one or two exceptions are entirely cartilaginous at birth and in which ossification appears normally within the first five years of life. These sixty-seven constitute approximately 80 per cent of those centers of the extremities of the left side of the body which appear postnatally. We have constructed norms for our group of the number of nuclei of ossification present at various periods during the first five years.

Subjects.—The children available for our study were so-called well children from the rural and metropolitan area near Yellow Springs, Ohio. There were 75 boys and 74 girls. They represented a fair economic cross section but were weighted more at the "middle class" level. Three Negro children (1 boy and 2 girls) were included.

Roentgenograms Used.—Roentgenograms were taken of the following areas of the left side of the body: shoulder, elbow, wrist and hand,

TABLE 1.—*List of Centers Counted (Total, Sixty-Seven)*

Shoulder	Coracoid	Femur	Proximal epiphysis
Humerus	Proximal medial epiphysis		Greater trochanter
	Proximal lateral epiphysis		Distal epiphysis
	Capitellum	Knee	Patella
	Medial epicondyle	Tibia	Proximal epiphysis
Radius	Proximal epiphysis		Distal epiphysis
	Distal epiphysis	Fibula	Proximal epiphysis
Hand	Capitatum		Distal epiphysis
	Hamatum	Foot	Cuboid
	Triquetrum		First cuneiform
	Lunate		Second cuneiform
	Navicula		Third cuneiform
	Greater multiangular bone		Navicula
	Lesser multiangular bone		Epiphysis of calcaneus
	5 distal phalangeal epiphyses*		5 distal phalangeal epiphyses*
	4 middle phalangeal epiphyses*		4 middle phalangeal epiphyses*
	5 proximal phalangeal epiphyses*		5 proximal phalangeal epiphyses*
	5 metacarpal epiphyses*		5 metatarsal epiphyses*

* Starred centers are those constituting group A, graphed in chart 4.

hip, knee (anteroposterior; lateral after 24 months), ankle and foot (anteroposterior; lateral after 48 months).

Complete sets of roentgenograms were taken at regular intervals. The thirteen age levels utilized in the current study were 1, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months. A total of 1,282 sets of plates have been examined, 1,022 (517 of girls and 505 of boys) of which were used to form the curves. A set of roentgenograms was eliminated (*a*) if incomplete, (*b*) if taken outside the time limit for each age level, i. e., plus or minus ten days from the child's interval date from 1 through 24 months or plus or minus twenty days from the child's interval date from 30 through 60 months, and (*c*) if the presence of three or more centers was questioned by two examiners.

Centers Counted.—A center was counted as soon as it cast a small shadow on the roentgen plate. The centers used in constructing our total number curve are shown in table 1.

Curves.—From these data we have made our curves of expectancy for the age of appearance of ossification centers. Separate curves were made for boys and girls. Table 2 illustrates the number of subjects available at each age level. Table 3 shows the number of different age levels at which each subject was used—showing that the average number

TABLE 2.—*Number of Subjects Studied at Each Age Level*

Age, Months	No. of Boys	No. of Girls	Age, Months	No. of Boys	No. of Girls
1	45	40	30	37	47
3	35	40	36	38	41
6	51	55	42	32	36
9	40	42	48	34	33
12	49	43	54	31	27
18	41	41	60	29	29
24	43	43			
Total				505	517

TABLE 3.—*The Number of Age Levels at Which Each Subject Was Studied*

Number of Times Examined	Boys	Girls	Number of Times Examined	Boys	Girls
1	6	6	8	7	10
2	2	0	9	9	10
3	4	2	10	4	3
5	12	6	11	3	4
6	6	6	12	4	3
7	10	15	13	3	2
Total number of individual subjects studied				75	74
Average number of times examined				6.7	7.0

TABLE 4.—*Mean Total Number of Centers on the Left Side of Body Ossified at Given Age Levels*

Age, Months	Boys		Girls	
	Mean Number	Standard Deviation	Mean Number	Standard Deviation
1	4.11	1.41	4.58	1.76
3	6.63	1.86	7.78	2.16
6	9.61	1.95	11.44	2.53
9	11.88	2.66	15.36	4.92
12	13.96	3.96	22.40	6.93
18	19.27	6.61	34.10	8.44
24	29.21	8.10	43.44	6.65
30	37.59	7.40	48.91	6.50
36	43.42	5.34	52.73	5.48
42	47.06	5.26	56.61	3.98
48	51.24	4.59	57.94	3.91
54	53.94	4.35	59.89	3.36
60	56.24	4.07	61.52	2.69

of times a subject was examined was approximately seven. Table 4 shows the mean number of centers ossified at given age levels, together with standard deviations. In charts 1 and 2 these values have been smoothed, and skeletal development as measured by this method is illustrated graphically.

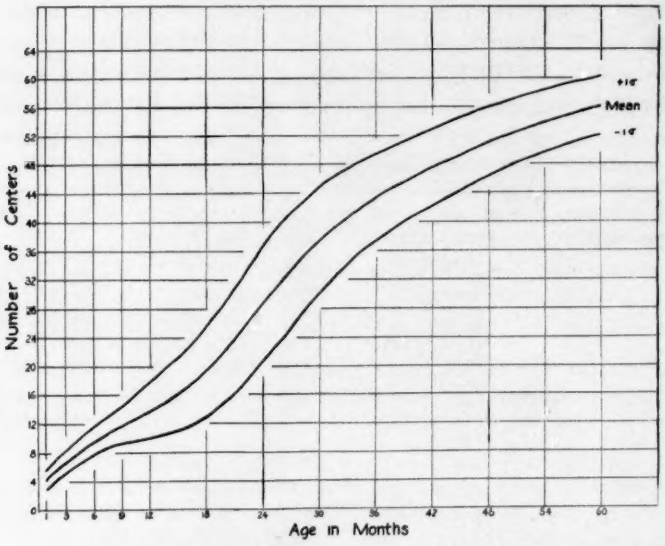


Chart 1.—Number of ossification centers (boys).

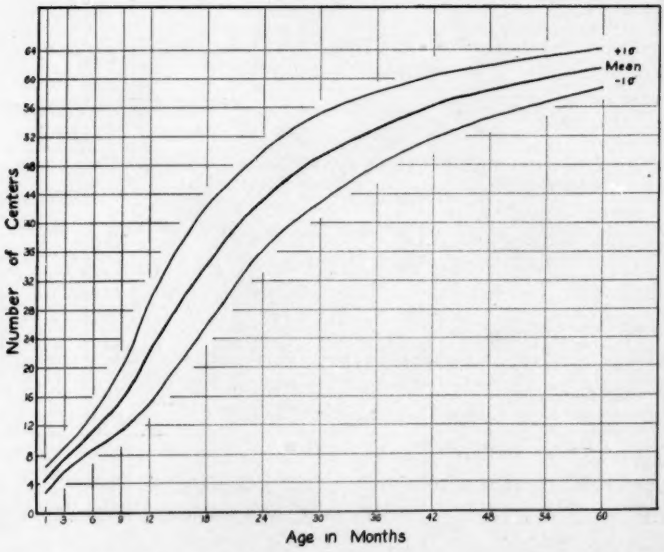


Chart 2.—Number of ossification centers (girls).

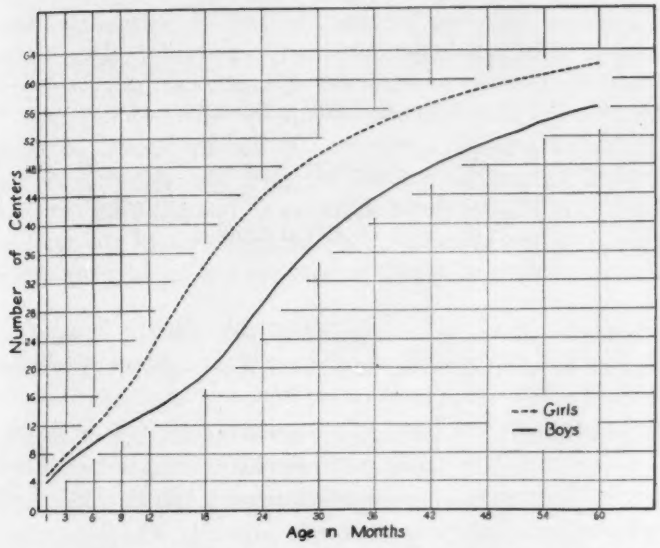


Chart 3.—Mean number of ossification centers (boys and girls).

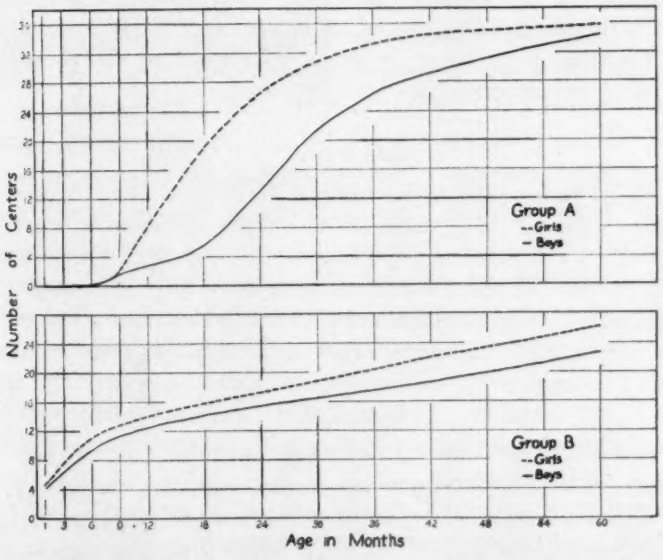


Chart 4.—Mean number of ossification centers grouped: Group A, metacarpal, metatarsal and phalangeal epiphyses; group B, epiphyses of carpal, tarsal and long bones.

COMMENTS

The significant difference between the rate of skeletal development of boys and of girls is brought out clearly (chart 3). This difference is pronounced whether the total number of centers or only those appearing in specific areas are considered (chart 4). It is of interest to note that the period of greatest acceleration in the ossification of epiphyses comes between 12 and 42 months for girls and between 18 and 48 months for boys. This acceleration makes a "hump" in the curve which is due entirely to the appearance of the epiphyses of the metacarpal, metatarsal and phalangeal bones, as can readily be seen by reference to chart 4.

For the past year we have been using this method in our routine assessments of physical growth, and to us it has shown the following advantages:

1. The growth which is measured is based on the time of appearance of the epiphyses of the left upper and lower extremities and is, therefore, not subject to the errors inherent in examining the growth of only a hand or a foot.

2. The method is rapid and objective, requiring little training or skill, and avoids the technical and subjective errors inherent in other methods.

3. It is the only method we have found in which the limit of error of each estimation is small enough to enable us to determine and express numerically the skeletal progress of an individual child at successive age levels. It makes no pretense, however, of measuring the progress of maturation of centers once they have appeared.

SUMMARY

A scale for rating progressive skeletal development of boys and girls from birth to the age of 5 years, based on data obtained in a study of longitudinal growth, has been presented. All joints of the left upper and lower extremities are given equal rating with the hand in appraising skeletal growth. Two additional curves for specific areas are also given.

The advantages of the scale are that no great skill is required to count the number of centers of ossification and that the results are rapidly and objectively achieved. It is a flexible and convenient method of evaluating skeletal age for correlation with other factors of growth, nutrition or environment.

The method is applicable only at the early age levels, since it is during this period that most of the centers appear.

Idell Pyle, Lois Hulstone and Robert Eastman read roentgenograms and worked on statistics. Mary Elizabeth Lipford assisted with the graphs.

BASAL METABOLISM OF TUBERCULOUS CHILDREN

IV. CHILDREN WITH PNEUMOTHORAX

ANNE TOPPER, M.D.
AND
HAROLD S. RUBIN, M.D.
NEW YORK

This paper reports the results of studies on the basal metabolism of afebrile children with the adult, or reinfection, type of pulmonary tuberculosis in whom pneumothorax therapy was instituted. The work is part of an extensive study of the basal metabolism of tuberculous children which is being made at Sea View Hospital.

One hundred and fourteen basal metabolism tests were made on 66 children. Their ages ranged from 7 years and 2 months to 16 years and 6 months. There were 49 girls and 17 boys. Since it was found that neither sex nor race significantly affected the results, a differentiation on these lines was not attempted.

Thirty of these children were studied before pneumothorax had been instituted and again at varying periods after the procedure. Thirty-six children were studied only after pneumothorax had been induced. In the entire series pneumothorax had been maintained for periods ranging from one month to three years and five months.

The children were afebrile during the period of study. The pulse rate and the erythrocyte sedimentation rate were studied in most of the cases. Thirty-five vital capacity tests were made for 31 of the children.

All the collected data may be seen in table 1. These data are summarized in table 2. The collected data for the 30 children who were studied both before and after pneumothorax had been instituted are summarized separately in table 3.

RESULTS

It may be seen from the tables that the basal metabolism was normal in the majority of cases before pneumothorax treatment was begun. The rate ranged from —2 to + 15 per cent. Since the children were all suffering from the adult type of tuberculosis, the finding of a

From the Pediatric Service of Dr. Bela Schick, Sea View Hospital, Staten Island, N. Y.

TABLE 1.—*Basal Metabolism of Tuberculous Children with Pneumothorax*

Subject	Sex	Age Yr.	Age Mo.	Height, Cm.	Sitting Height, Cm.	Weight, Kg.	Pulse Rate	Erythrocyte Sedimentation Rate, Mm. in 1 Hr.	Basal Metabolism, Total Calories	Basal Metabolic Rate, %	Vital Capacity, Cc.	Age at Which Pneumothorax Was Instituted Yr.	Age at Which Pneumothorax Was Instituted Mo.	Time Interval After Pneumothorax Was Instituted
D. A.	F	15	1	155	88	65	108	25	1,649	+ 6	.....	15	1	
		15	6	155	88	66	84	24	1,456	— 6	.....	..	..	5 months
A. A.	M	14		146	80	48	98	23	1,313	+ 3	.....	14	..	
		14	8	148	82	49	84	13	1,205	—11	1,800	..	..	8 months
E. A.	F	12		130	70	26	100	..	1,127	+15	.....	12	6	
		14		143	77	44	72	12	1,180	— 1	.....	..	..	1½ years
H. A.	M	13		155	80	41	84	12	1,183	— 8	1,700	12	8	4 months
L. B.	F	12	6	154	80	40	108	8	1,382	+ 8	.....	12	7	
		13	7	156	82	43	90	5	1,284	— 4	2,200	..	..	1 year
R. B.	F	14	4	154	82	50	110	38	1,548	+15	.....	14	5	
		14	11	155	83	54	68	15	1,272	— 8	.....	..	..	6 months
S. B.	M	14	4	159	82	55	90	25	1,490	+11	.....	14	4	
		15	1	161	84	64	68	8	1,328	— 6	1,500	..	..	9 months
E. B.	F	12	8	146	77	31	90	..	1,116	— 7	.....	12	5	3 months
H. C.	F	15	10	155	84	40	96	50	1,321	— 7	1,200	14	10	1 year
T. C.	M	14	3	172	85	63	90	3	1,394	— 4	1,600	13	7	8 months
P. C.	M	12	4	137	70	31	90	34	1,123	+14	.....	12	5	
		13	6	143	77	37	84	9	1,164	— 2	.....	..	..	13 months
		14	6	151	80	39	68	12	1,114	—13	1,000	..	..	2 years 1 month
W. C.	M	14	11	158	86	48	98	..	1,675	+14	.....	15	..	
		15	6	160	88	54	84	10	1,639	+ 6	.....	..	..	6 months
M. D.	F	14	3	156	83	46	76	9	1,238	—11	.....	13	9	6 months
M. D.	F	14	8	155	82	48	84	28	1,360	+ 1	.....	13	8	1 year
R. D.	M	13	10	162	87	55	90	2	1,579	+ 4	.....	13	10	
		14	5	164	88	60	80	9	1,512	— 2	1,800	..	..	7 months
A. D.	F	13		154	84	46	100	12	1,460	+ 3	.....	12	..	1 year
		15	5	160	87	52	72	10	1,425	— 6	.....	..	..	3 years 5 months
A. D.	F	12	5	151	80	40	80	17	1,315	+ 3	.....	11	10	7 months
I. D.	F	15	11	168	84	54	90	..	1,289	— 8	.....	15	8	3 months
L. F.	F	15		158	87	51	80	..	1,473	— 2	1,600	13	7	1 year 5 months
A. F.	M	15	9	160	88	49	64	5	1,320	—17	.....	15	..	9 months
F. F.	F	9	9	132	70	26	88	4	902	+ 1	.....	9	..	9 months
		10	5	136	73	23	72	7	1,034	— 3	1,300	..	..	1 year 5 months
M. G.	F	9	8	135	68	24	120	..	918	— 1	.....	9	11	
		10	2	136	69	27	72	14	939	— 1	.....	..	..	8 months

A. H.	F	13		152	79	42	104	44	1,229	+ 4	.....	13	..	
		15		159	82	41	88	12	1,147	—15	1,300	..	..	2 years
		15	9	160	83	41	88	..	1,166	—16	900	..	..	2 years 9 months
V. H.	F	13	10	167	88	54	98	..	1,642	+ 6	.....	13	10	
		14	4	169	90	53	88	15	1,577	— 3	.....	..	..	6 months
E. H.	F	13		150	78	42	112	39	1,361	+12	.....	13	..	
		14	3	158	80	50	90	35	1,267	— 1	.....	..	..	1 year 3 months
B. H.	F	13	11	170	85	45	100	..	1,355	— 6	.....	14	..	
		14	6	172	90	50	90	7	1,390	—14	.....	..	..	6 months
D. H.	M	10	6	131	68	30	108	..	928	+ 1	.....	10	7	
		11	6	136	72	33	88	..	925	—11	1,300	..	..	11 months
A. H.	F	14	8	145	77	44	92	..	1,207	+ 2	.....	14	8	
		15	1	146	77	46	80	18	1,197	+ 1	.....	..	..	5 months
A. J.	F	12		156	80	38	102	19	1,210	— 5	.....	12	7	
		14		165	84	38	88	..	1,064	—24	900	..	..	1 year 5 months
R. J.	F	13		150	81	51	96	30	1,460	+11	.....	13	..	
		14		162	82	58	106	48	1,542	+15	.....	..	..	1 yr., pleural effusion
		14	3	162	82	58	90	..	1,435	+ 7	.....	..	..	1 yr. 3 mo., clearing
		14	8	162	84	63	92	19	1,400	— 1	.....	..	..	1 yr. 8 mo., small amount of fluid
C. J.	M	11	8	135	70	62	88	40	1,068	+ 9	.....	11	8	
		12	4	137	73	63	84	29	1,035	— 3	.....	..	..	8 months
M. J.	F	15	9	163	85	46	80	26	1,286	—11	.....	14	9	1 year
A. L.	M	14	8	163	83	45	86	11	1,499	+ 9	.....	14	7	1 month
J. L.	M	14	9	156	80	42	96	..	1,416	+10	.....	14	9	
		15		156	80	42	94	..	1,252	— 2	1,900	..	..	3 months
E. L.	F	9	2	133	70	31	90	12	1,046	+ 7	700	8	8	6 months
J. M.	F	14	1	163	86	47	80	7	1,363	— 6	2,200	12	..	2 years 1 month
F. M.	M	15	5	170	90	58	78	6	1,458	—10	2,000	14	..	1 year 5 months
		15	9	172	92	57	70	9	1,478	—14	1,500	..	..	1 year 9 months
F. M.	F	10	4	130	68	27	100	5	1,017	+10	.....	10	8	
		10	10	132	70	..	....	..	954	— 3	.....	..	..	2 months
		12		142	78	32	90	6	1,000	—18	2,000	..	..	1 year 4 months
		13		150	80	38	80	..	1,025	—20	1,700	..	..	2 years 4 months
I. M.	F	14		152	83	50	99	12	1,323	— 4	.....	13	6	6 months
M. M.	F	14	9	158	82	58	78	..	1,449	+ 3	.....	14	..	9 months
		16	5	160	85	61	68	..	1,368	— 5	.....	..	..	2 years 5 months
J. M.	F	15	1	156	83	58	100	..	1,578	+15	.....	15	1	
		15	4	156	83	60	88	..	1,464	+ 6	.....	..	..	3 months
		15	10	158	86	61	84	..	1,452	— 2	.....	..	..	9 months
C. M.	M	13	5	159	84	46	80	..	1,542	+ 5	2,000	12	..	1 year 5 months
D. M.	F	15		151	81	50	80	7	1,321	+ 1	.....	14	3	9 months
G. M.	F	15		152	83	40	90	54	1,241	—10	.....	15	5	
		16	6	157	85	42	84	31	1,003	—30	1,600	..	..	1 year 1 month, marked undernutrition
I. M.	M	13	10	142	75	32	80	38	1,145	+ 2	.....	13	8	2 months
		14	2	144	76	37	72	12	1,186	+ 1	1,600	..	..	6 months

TABLE 1.—*Basal Metabolism of Tuberculous Children with Pneumothorax—Continued*

Subject	Sex	Age Yr.	Age Mo.	Height, Cm.	Sitting Height, Cm.	Weight, Kg.	Pulse Rate	Erythrocyte Sedimentation Rate, Mm. in 1 Hr.	Basal Metabolism, Total Calories	Basal Metabolic Rate, %	Vital Capacity, Cc.	Age at Which Pneumothorax Was Instituted Yr.	Age at Which Pneumothorax Was Instituted Mo.	Time Interval After Pneumothorax Was Instituted
R. M.	F	14		161	85	56	84	..	1,329	— 8	2,100	13	..	1 year
		15	3	169	90	57	70	16	1,267	—15	1,800	..	..	2 years 3 months
D. M.	F	7	2	126	69	25	96	27	1,086	+14	.....	8	..	
		8	10	134	73	34	80	3	1,044	— 2	.....	..	..	10 months
E. N.	F	14	7	150	82	50	80	..	1,207	—10	1,100	13	10	9 months
R. N.	F	14	4	156	85	37	80	2	1,109	—23	.....	13	2	1 year 2 months
A. O.	F	15	2	151	80	44	100	..	1,279	— 1	.....	15	2	
		15	6	152	80	47	80	..	1,103	—14	.....	..	..	4 months
F. P.	F	15	7	161	84	45	68	18	1,145	—20	1,000	14	7	1 year
M. R.	F	14	5	169	85	53	78	6	1,402	— 3	1,700	13	7	10 months
T. R.	F	14	8	151	80	45	90	20	1,355	+ 6	.....	14	5	3 months
		16	8	164	84	50	80	14	1,345	— 5	.....	..	..	2 years 3 months
R. R.	M	13	9	165	83	45	90	11	1,411	+ 2	.....	14	..	
		14	1	169	85	48	92	..	1,511	+ 5	2,100	..	..	1 month
		14	10	176	90	54	84	20	1,486	— 8	.....	..	..	10 months
		15	1	177	90	59	78	..	1,457	—10	1,500	..	..	1 year 1 month
Y. S.	F	14		154	82	53	78	..	1,296	— 3	.....	13	9	3 months
V. S.	M	15	5	154	82	48	90	45	1,460	+ 8	.....	15	5	
		16	5	156	84	50	68	10	1,246	—12	1,300	..	..	1 year
A. S.	F	13		162	85	67	105	27	1,653	+14	.....	13	..	
		14		164	86	70	80	12	1,440	— 2	.....	..	..	1 year
S. S.	F	14	3	157	81	62	88	22	1,464	+12	.....	14	4	
		15	3	160	85	68	78	14	1,264	—13	900	..	..	11 months
E. S.	F	16	4	164	84	58	76	5	1,464	+ 4	.....	15	10	6 months
I. T.	F	13	5	158	82	43	100	..	1,364	+ 1	.....	13	3	2 months
Y. T.	F	14		160	83	43	104	38	1,357	— 2	.....	14	4	
		14	9	161	83	44	82	..	1,257	— 9	2,000	..	..	5 months
L. W.	F	13	6	158	85	48	90	14	1,248	—13	.....	12	6	1 year
L. W.	F	11	11	148	77	32	100	..	1,234	+ 4	.....	11	10	1 month
M. W.	F	15	2	156	84	50	80	7	1,310	— 7	1,400	14	9	5 months
G. Z.	F	13		143	80	50	76	15	1,205	— 6	.....	12	..	1 year
F. Z.	M	9	1	127	70	28	80	21	1,080	+10	.....	9	4	
		9	5	127	70	27	82	..	1,045	+ 7	.....	..	..	1 month
		9	8	128	70	27	78	8	1,086	+ 6	.....	..	..	4 months

normal metabolic rate was not surprising. Most investigators [1] agree that the basal metabolism in this type of tuberculosis is for the most part normal unless severe toxemia is present. Great toxic destruction of body protein tends to increase the basal metabolic rate.[2]

The pulse rate in these cases ranged from 80 to 120 per minute before therapy. The erythrocyte sedimentation rate ranged from 5 to 54 mm. per hour. In the majority of cases there was an increase.

It may be seen from table 2 that after pneumothorax was induced the basal metabolism, the pulse rate and the sedimentation rate showed a definitely lowered trend. In 30 cases in which pneumothorax had been instituted within six months, the average basal metabolic rate was

TABLE 2.—*Summary of Studies on Basal Metabolism During Pneumothorax Treatment*

	No. of Tests Made	Range of Basal Metabolic Rates, %	Average Basal Metabolic Rate, %	Average Pulse Rate
Before pneumothorax was instituted	30	+15 to — 2	+ 7	97
1-6 months later	30	+10 to —14	— 3	84
6-12 months later	30	+ 7 to —17	— 5	81
More than 1 year later	24	+ 7 to —30	—10	79

TABLE 3.—*Basal Metabolic Rates of 30 Children Studied Before and After Pneumothorax Was Instituted*

	Range of Basal Metabolic Rates, %	Average Basal Metabolic Rate, %	Average Pulse Rate
Before pneumothorax was instituted	— 2 to +15	+ 7	95
1-3 months later	— 6 to +10	+ 1	
3-6 months later	—14 to + 6	— 5	
6-9 months later	— 2 to —11	— 4	81
9-12 months later	— 2 to —12	— 7	
More than 1 year later	— 1 to —30	—12	

—3 per cent and the range was from + 10 to —14 per cent. The average pulse rate was 84 per minute. The sedimentation rate in this group ranged from 5 to 24 mm.

1. Kocher, R. A.: California State J. Med. **19**:430, 1921. McCann, W. S., and Barr, D. P.: Am. Rev. Tuberc. **5**:870, 1922. Gekler, W. A., and Weigel, B. J.: Southwestern Med. **10**:221, 1926. Frank, L. W., and Safarik, L. R.: Colorado Med. **25**:61, 1928. Topper, A., and Rosenberg, H.: Basal Metabolism of Tuberculous Children, Am. J. Dis. Child. **52**:266 (Aug.) 1936.

2. McCann, W. S., and Barr, D. P.: Clinical Calorimetry: Metabolism in Tuberculosis, Arch. Int. Med. **26**:663 (Dec.) 1920. Grafe, E.: München. med. Wchnschr. **67**:1081, 1920. McMahon, A., and Klein, H. A.: J. Missouri M. A. **26**:586, 1929.

There were 30 cases in which pneumothorax had been maintained from six months to a year. In this group, the metabolic rate ranged from + 7 to —17 per cent, the average being —5 per cent. The pulse rate averaged 81 per minute. The sedimentation rate ranged from 3 to 29 mm. except in 1 case, in which it was 50 mm.

In 24 cases in which pneumothorax had been instituted more than a year previously, the average basal metabolic rate was —10 per cent and the range was from + 7 to —30 per cent. The average pulse rate in this group was 79 per minute. The range of the sedimentation rate was from 7 to 35 mm.

These figures seem to indicate that the basal metabolism is decreased by pneumothorax and still further lowered the longer the pneumothorax is maintained. Since no figures on the basal metabolism before treatment were available for 36 of the children, we desired to eliminate the element of chance sampling in evaluating the low figures obtained with pneumothorax. We therefore analyzed separately the 30 cases in which the metabolism had been studied both before and after pneumothorax treatment had been instituted. In this group the basal metabolic rate before treatment was instituted ranged from + 15 to —2 per cent. The average was + 7 per cent. When pneumothorax had been maintained from one to three months, a slight decrease in the metabolic rate was noted. The range was from + 10 to —6 per cent and the average rate + 1 per cent.

Those children who were retested after pneumothorax had been maintained from three to six months showed an average metabolic rate of —5 per cent. The range too was lower, from + 6 to —14 per cent. For the children studied six to nine months after collapse therapy had been instituted the range was still lower, viz., —2 to 11 per cent, with an average of —4 per cent. Children in whom pneumothorax was maintained for from nine months to a year averaged —7 per cent in their basal metabolic rate, the range being from —2 to —12 per cent. The children in whom pneumothorax had been induced more than a year previously showed a range of metabolic rates from —1 to —30 per cent, the average having fallen to —12 per cent.

Although the number of cases thus studied is small, the results are convincing because of their consistency. The pulse rate seemed to be definitely slower after induction of pneumothorax, and even the sedimentation rate seemed to show some decrease. Evidently the institution of pneumothorax lowers the heat production of tuberculous children. The decrease in the basal metabolism was only slight in cases in which pneumothorax had been recently instituted, but the longer the collapse was maintained the lower the metabolic rate seemed to fall.

The decrease in the metabolism may perhaps be explained partly by a decrease in the activity of the collapsed lung, with a decrease in the

demands for oxygen by the tissues, and partly by a lessening of the spread of toxins, due to the immobilization of the diseased lung.

The vital capacity, when studied, was for the most part found to be low. The range was from 700 to 2,200 cc., the average of the 35 tests being, 1,550 cc. It is known that the vital capacity is low in pulmonary tuberculosis, partly because of an increase in the volume of residual air and partly because of a decrease in the elasticity and destruction of lung tissue.[3]

In cases of pneumothorax there is a still further lowering of the vital capacity. Myers [4] found the vital capacity to be 49 per cent of the normal in such cases. Stewart [5] and Edwards and Wilson [6] have computed the normal vital capacity according to standing height, since they found this a more accurate standard than either weight or surface area. Measured by this standard, our children, who averaged 158 cm. in height, should have had an average vital capacity of 2,450 cc. Their determined average was 1,550 cc., a decrease of 37 per cent from the expected normal.

The lowered vital capacity may be an additional factor in the lowered basal metabolism found in these children.

SUMMARY

One hundred and fourteen basal metabolism tests were made on 66 afebrile children with the adult type of pulmonary tuberculosis in whom pneumothorax had been instituted.

Thirty of these children were studied both before and after the procedure. Thirty-six were studied only after.

The average basal metabolic rate before pneumothorax was instituted was + 7 per cent (von Pirquet standard based on sitting height [7]).

For children in whom pneumothorax had been maintained for from one to six months, the average basal metabolic rate was —3 per cent.

For children in whom pneumothorax had been instituted from six to twelve months previously, the average rate was —5 per cent.

For children in whom collapse therapy had been maintained for over a year, the average rate was —10 per cent.

---

3. Siebeck, R.: Deutsches Arch. f. klin. Med. **100**:204, 1910. Dreyer, G., and Burrell, L. S. T.: Lancet **2**:374, 1922.

4. Myers, J. A.: Vital Capacity of the Lungs, Baltimore, Williams & Wilkins Company, 1925, p. 51.

5. Stewart, C. A.: Am. Rev. Tuberc. **13**:272, 1926.

6. Edwards, D. J., and Wilson, M. G.: Analysis of Some Factors of Variability in the Vital Capacity Measurements of Children, Arch. Int. Med. **30**: 638 (Nov.) 1922.

7. von Pirquet, C.: An Outline of the Pirquet System of Nutrition, Philadelphia, W. B. Saunders Company, 1922.

The pulse rate and the erythrocyte sedimentation rate seemed to be somewhat lower after pneumothorax had been induced than before.

In order to eliminate the possibility of chance sampling, the rates of the 30 children who had been studied before and after the procedure were analyzed separately. The average metabolic rate was + 7 per cent before pneumothorax was instituted. Studied again within three months, it had fallen to + 1 per cent. Between three and six months later it was — 5 per cent. The children studied from six to nine months later showed an average metabolic rate of —4 per cent. For those in whom pneumothorax had been maintained from nine months to a year, the average rate had fallen to — 7 per cent, and for those studied after pneumothorax had been maintained for more than a year, the average rate was —12 per cent.

CONCLUSIONS

These studies indicate that the basal metabolism is lowered by pneumothorax therapy. The longer the pneumothorax is maintained the lower the metabolism seems to fall.

Studies of the vital capacity gave results 37 per cent lower than the expected normal.

The lowering of the basal metabolism can probably be explained on the basis of a lowering of the vital capacity, a lessening of the spread of toxins due to the immobilization of the diseased lung and a decrease in the oxygen requirements of the the collapsed lung tissue.

FACTORS AFFECTING RETENTION OF NITROGEN AND CALCIUM IN PERIOD OF GROWTH

I. EFFECT OF THYROID ON NITROGEN RETENTION

J. A. JOHNSTON, M.D.
AND
JOHN W. MARONEY, M.D.
DETROIT

One of the characteristics of growth is the retention within the organism of what Robertson referred to as the "substrates" of growth, and of these the two subjected to the most frequent analysis have been nitrogen and calcium. As a measure of growth of active protoplasmic tissue and of the bony skeleton, weight is notoriously unreliable, and height is significant only over long periods. We have previously shown prolonged gain in weight with a negative nitrogen balance and retention of this substance for comparatively long periods with a failure to gain. Accordingly, in attempting to evaluate the effect of thyroid on growth we have used the balance method for these two substances under a variety of conditions and with variations in dosage as criteria. While originally it was planned to present both sets of material together, it has become evident that the behavior of the one substance does not necessarily parallel that of the other, and accordingly a division has been made in the treatment of the data. Certain physiologic principles should be recalled in any interpretation of balance studies such as these. There would seem to be a definite limit to the storage of nitrogen, beyond which attempts to effect increases with increments in the diet not only are futile but result in diminished retention. Secondly, age is a conditioning factor, the ability to retain being strikingly high during the periods of rapid growth stressed by Robertson.[1] Thirdly, the effect of glandular substance will be conditioned by the presence or absence of a defect, the effect being notably different in animals deprived of the gland secreting the hormone and in normal animals.

In hypothyroid states the administration of thyroid has been shown to be followed by an increased storage of nitrogen after an initial nega-

From the Department of Pediatrics, Henry Ford Hospital. One of a series of metabolism studies made in connection with the study of childhood tuberculosis conducted for the Society of St. Vincent de Paul under the joint auspices of the Henry Ford Hospital and the Children's Fund of Michigan.

1. Robertson, T. B.: The Chemical Basis of Growth and Senescence, Philadelphia, J. B. Lippincott Company, 1923.

tive stage due to a release of "rest" nitrogen.[2] In hyperthyroid states a high nitrogen loss has been shown to be preventable by a high intake of sugar or fat, thus excluding a specifically "toxic" effect of thyroid on nitrogen.[3] In normal subjects to whom thyroid was given, Janney,[2a] studying 2 12 year old girls, and Deuel and his associates,[4] studying an adult, found a diminished retention; the doses used were comparatively large. Weymuller and his associates,[5] studying infants, found that the rise in metabolism induced by large doses of thyroid was not accompanied with a corresponding rise in nitrogen excretion. The balances showed little change; on a percentage basis there was an actual fall of 1.9 per cent in the calories derived from combustion of protein. Topper and Cohen [6] reported an interesting group of children who failed to show a rise in basal metabolism during thyroid therapy but did show a spurt in growth, and they suggested that the effect of thyroid varied with the phase of growth and that this effect in childhood was essentially anabolic. Such a concept should involve an increased retention of nitrogen, though this effect need not necessarily be a specific one. Dorff,[7] reporting his own experience with a group of children in whom growth was stimulated by administration of thyroid although they lacked the gross physical changes usually associated with hypothyroidism, suggested that the cases of Topper and Cohen were examples of "masked hypothyroidism." In the light of what we feel is evident from the material presented here Dorff's doses (of a "standard" substance) in the 4 cases cited seemed large—1 to 5 grains (0.06 to 0.32 Gm.) in the first case, 2½ grains (0.16 Gm.) in the second, 1½ to 3 grains (0.09 to 0.19 Gm.) in the third and ½ to 2 grains (0.03 to 0.13 Gm.) in the fourth. The ages of the children ranged from 6 to 8 years.

2. (*a*) Janney, N. W.: Studies in Thyroid Therapy, Arch. Int. Med. **22**:187 (Aug.) 1918. (*b*) Boothby, W. M.; Sandiford, I.; Sandiford, K., and Slosse, J.: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects, Tr. A. Am. Physicians **40**:195, 1925. (*c*) DuBois, E. F.: Metabolism in Exophthalmic Goiter, Arch. Int. Med. **17**: 915 (June) 1916.

3. Boothby, W. M., and Sandiford, I.: The Total and the Nitrogenous Metabolism in Exophthalmic Goiter, J. A. M. A. **81**:795 (Sept. 8) 1923.

4. Deuel, H. J., Jr.; Sandiford, I.; Sandiford, K., and Boothby, W. M.: The Effect of Thyroxin on Respiratory and Nitrogen Metabolism of a Normal Subject Following Prolonged Nitrogen-Free Diet, J. Biol. Chem. **76**:407 (Feb.) 1928.

5. Weymuller, L. E.; Wyatt, T. C., and Levine, S. Z.: Respiratory Metabolism in Infancy and Childhood: XIV. The Effect of Thyroid Therapy on the Metabolism of Protein in Normal Infants, Am. J. Dis. Child. **43**:1544 (June) 1932.

6. Topper, A., and Cohen, P.: The Effect of Thyroid Therapy in Children, Am. J. Dis. Child. **35**:205 (Feb.) 1928.

7. Dorff, G. B.: Masked Hypothyroidism in Children, J. Pediat. **6**:788 (June) 1935.

PLAN OF STUDY AND METHODS

With the exception of 1 cretin, on whom merely sporadic determinations of the basal metabolic mixture were made, continuous balances were determined with a series of six rotating standard diets in which the calories were derived thus: 15 per cent from protein, 35 per cent from fat and 50 per cent from carbohydrate. Where "standard diet 1-6" is mentioned in a table, the nitrogen content was determined weekly from an aliquot sample of each day's diet; where this designation does not appear, the figure used for dietary nitrogen was obtained from an analysis of fifty entire meals digested in sulfuric acid and analyzed by the Kjeldahl-Gunning method. With this group, when the source of nitrogen was mixed the figure obtained by analysis exceeded the calculated figure from standard food tables by 11.75 per cent; when the source was milk or eggs the variation was negligible.

Determinations of basal metabolism were made by the gasometer method. The accuracy of analysis of the expired air was checked by frequent analysis of the outside air. The results were calculated from the oxygen consumption and the total respiratory quotient, though of course for the first cretin the nonprotein quotient was determined. The standards used were those of Boothby and Sandiford, but the basal calories for twenty-four hours were recorded also.

Two preparations of thyroid were used, those of Burroughs, Wellcome and Company and Parke, Davis and Company. It has been stated that the strength of the former is one-fifth that of the U. S. P. standard, but it is claimed by Burroughs, Wellcome and Company that it is two-fifths. We doubt that the effect parallels iodine content, and it is our impression that the preparation is at least two-fifths as strong as the Parke, Davis and Company preparation.

FINDINGS

Cretinism.—Subject 1.—A. V. (chart 1 and table 1) was an 11 year old cretin on whom merely sporadic observations of the basal metabolic mixture were made throughout a period when the basal metabolic rate was being brought from —35 to —12 per cent with thyroid and then permitted to decline to the original level without treatment. The observation covered five months. During the first three months the diet was only approximated, though on the night preceding a metabolic observation for which the urine was to be collected throughout the morning, an accurately weighed evening meal was taken; during the latter three months of the study the diet was constant throughout, as indicated in the table. The basal metabolic mixtures were determined from a nonprotein respiratory quotient, for the calculation of which the urinary nitrogen per hour was estimated from the morning's excretion after the first specimen was discarded. Table 1 and chart 1 bring out the decline in the percentage of calories derived from protein and carbohydrate with the reciprocal rise in the percentage derived from fat during the administration of thyroid and the reversal of this picture with the discontinuance of thyroid. Considering the fact that a certain fraction of the large amounts of nitrogen appearing in the urine when thyroid is first given may be in the nature of "rest" nitrogen, the conventional calculation of the protein of the metabolic mixture is questionable, but this criticism would not apply to the increasing amounts noted in the after-period, when thyroid has been discontinued.

Subject 2.—D. E. (chart 2 and table 2) was a typical cretin, who had been under treatment with thyroid for ten years. Treatment was discontinued and the basal metabolism allowed to fall as low as —30 per cent and a continuous nitrogen balance determined for fifteen months, data on five of which are summarized and included in table 2 and chart 2. Though a fixed measured diet

TABLE 1.—*Effect of Thyroid on Basal Mixture of Subject 1 (A. V., Cretin)*

Date	Weight, Pounds	Calories per Hour	Protein		Fat		Carbohydrate		Basal Metabolic Rate	Respiratory Quotient	Comment
			Gm.	Calories, Percentage	Gm.	Calories, Percentage	Gm.	Calories, Percentage			
3/18/31	81	32.8	3.96	50.3	0	0	3.9	49.7	—35	.94	Diet, approximately 2,000 calories; protein 13 per cent (67 Gm.); fat 51 per cent, and carbohydrate 36 per cent; supper night before test weighed: protein 22 Gm.; fat 38 Gm., and carbohydrate 38 Gm.
3/19–3/25											Dried thyroid, (B. W.), 3 grains (0.195 Gm.) a day
4/ 3	91	35.9	3.48	40	0.74	19.5	3.50	40.5	—32	.86	
4/ 4–5/ 4											Dried thyroid extract (B. W.), 6 grains (0.39 Gm.) a day
4/16	88½	45.7	3.50	32	2.57	52	1.72	16	—12	.79	
5/ 4											Thyroid therapy discontinued
5/27	91¼	40.8	1.73	18	2.78	64	1.86	18	—23	.77	
6/ 4											Weighed diet, 1,485 calories: protein 13 per cent (48 Gm.); fat 46 per cent; carbohydrate 41 per cent *
6/18	95	36.1	2.62	29	1.98	52.5	1.60	18.5	—32	.86	
7/22	95	34.0	2.56	32	1.31	36	2.66	32	—35	.83	
8/19	96	33.2	3.30	41	0.13	4	4.39	55	—37	.91	

* Standard experimental diet.

was offered throughout, the patient consistently refused a part of it when she was not receiving thyroid. The refused portion as well as that eaten was analyzed for nitrogen. The negative balances of the second and third periods may be explicable on the basis of the disgorgement of "rest" nitrogen, as suggested by Boothby. For six weeks, from April 10 to May 24, however, the chart shows a steady increase in retention paralleling the rise in the basal metabolism and continuing beyond the peak of this, followed by a steady decline in the retention from May 25 through July 19, with a falling metabolic rate. Much of the increased retention is directly referable to an increase in the intake, although the second lowest output in the urine occurred with the peak in the metabolism.

The conclusion from the first case is that thyroid exerts a direct anabolic effect with an actual reduction in the output of urinary nitrogen; the second case does not bear this out entirely; here the effect was

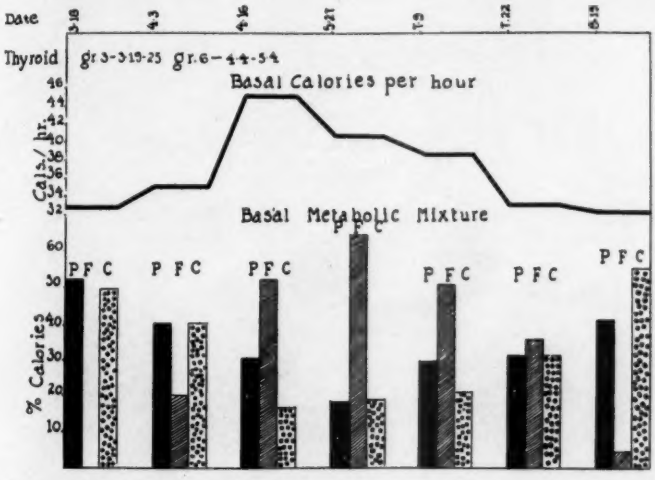


Chart 1 (A. V., cretin).—The basal metabolic mixture at various levels of metabolism during the administration of and after the discontinuance of thyroid. The solid black bar represents protein, the cross hatching carbohydrate and the stippling fat. Protein was calculated from the urine passed from 8 a. m. to 12 noon on the morning of the determination of metabolism, a fixed measured diet having been used for the evening meal. *P*, *F* and *C* in this and subsequent charts indicate protein, fat and carbohydrate, respectively.

anabolic but could be attributed largely to an increased intake and presumably to the sparing effect on nitrogen of the improved utilization of the other items of the metabolic mixture.

Mild Hyperthyroidism.—SUBJECT 3.—L. L. (chart 3 and table 3) was a 14 year old girl showing mild hyperthyroidism at puberty. She was admitted because of nervousness, tremor and a frank enlargement of one lobe of the thyroid, with diffuse enlargement of the rest of the gland. Her metabolic rate varied from + 24 to —2 per cent and did not appear to be greatly influenced by the amount of activity which she was permitted. The condition ultimately subsided with rest in bed and iodine therapy. During the period in which iodine was administered,

TABLE 2.—*Effect of Thyroid on Nitrogen Balance of Subject 2 (D. E., Cretin)*

Date	Diet †	Nitrogen, Mg.				Date	Basal Metabolic Rate	Respiratory Quotient	Basal Calories *	Height, Inches	Weight, Pounds	Medication
		Intake	Urine	Stool	Balance							
2/16–24/36	1,400 calories	8.27	7.00	0.80	+0.47	2/18	—30	83	836	52¼	76½	2/20–3/24
	P 52.4 Gm.					2/21	—27	84	893		76	Thyroid (B. W.), 1 grain
2/25–3/ 4	F 54.4 Gm.	8.33	8.21	0.88	—0.76	2/25	—27	84	887		77½	
	C 175 Gm.					2/28	—30	82	835		76¼	
						3/ 3	—25	85	905		77½	
3/ 5–13		7.97	8.73	1.14	—1.90	3/ 6	—23	83	920		75½	
3/14–22		7.19	5.11	0.81	+1.27	3/23	—19	79	978	52½	76	
3/23–31		8.36	6.44	0.75	+1.17	4/ 2	—17	84	982		75	3/25–5/22
4/ 1– 9		7.53	6.80	0.64	+0.09	4/ 8	—16	87	982		75	Thyroid (B. W.), 1½ grain
4/10–18		8.47	8.27	1.03	—0.83	4/14	—16	87	1,002		76	
4/19–28		8.62	7.92	1.23	—0.53	4/21	—12	83	1,039	52¾	75	
						4/28	— 5	80	1,118		72	
4/29–5/ 7		7.80	6.89	1.28	—0.37	5/ 5	— 5	84	1,127		75	
5/ 8–16		8.27	5.93	1.14	+1.20	5/13	± 0	80	1,212	53	73	
5/17–24		10.10	7.14	1.06	+1.90	5/18	— 4	83	1,166		74½	
5/25–6/ 2		10.06	7.78	1.14	+1.14	6/ 1	— 6	81	1,147		76½	
6/ 3–11		9.30	8.12	0.95	+0.23	6/13	—16	82	1,001		75	
6/12–21		9.12	7.41	0.95	+0.76	6/18	—19	88	971		78	
						6/20	—21	87	972	53¼	78¼	
6/22–30		8.05	6.91	1.07	+0.07	6/25	—18	89	1,013		78	
7/ 1–11		8.71	7.21	1.12	+0.38	7/ 2	—20	82	958		76½	
						7/ 9	—26	82	912		77	
7/12–19		7.80	6.74	1.31	—0.25	7/16	—26	89	912		77¾	

* In the accompanying chart two or more determinations of basal metabolism falling within the same nine day period of collection have been averaged.

† *P* indicates protein; *F*, fat, and *C*, carbohydrate.

the rise and fall in metabolism were paralleled directly by a rise and fall in the nitrogen balance. Because of unusual cooperation, the intake was constant throughout. During the latter half of the period of observation, the balance remained slightly positive and seemed independent of the fluctuations in the metabolic rate.

A premenarcheal rise and a subsequent fall in the basal metabolic rate have been demonstrated.[8] Studies of the rate of growth by Boas [9] and by Shuttleworth [10] have shown a steadily mounting rate of growth

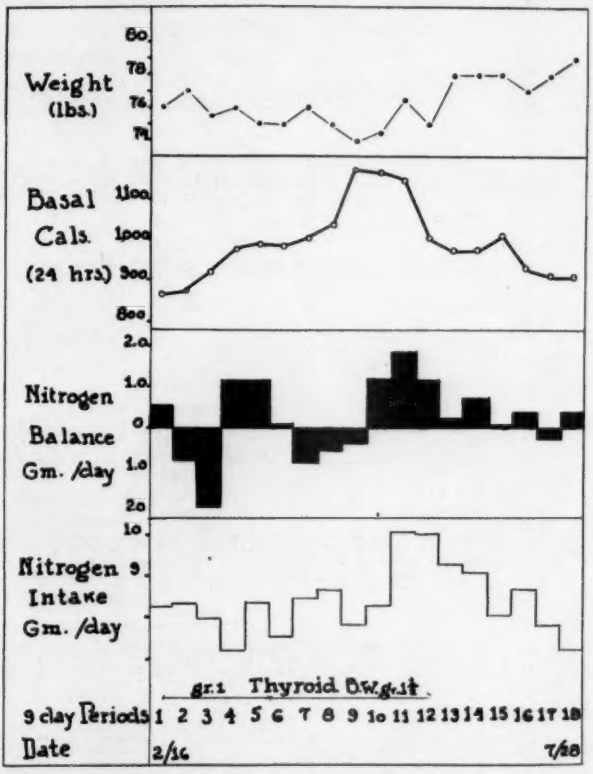


Chart 2 (D. E., cretin).—A continuous nitrogen balance study for five months during the administration of and after the discontinuance of thyroid.

preceding the menarche, followed by a rapidly declining rate following the first menstrual period. These two sets of findings should correlate metabolism and retention directly and suggest that the higher metabolic

8. Topper, A., and Mulier, H.: Basal Metabolism of Normal Children: Puberty Reaction, Am. J. Dis. Child. **43**:327 (Feb.) 1932.

9. Boas, F.: Studies in Growth, Human Biol. **3**:307 (Sept.) 1932.

10. Shuttleworth, F. K.: Sexual Maturation and the Physical Growth of Girls Age Six to Nineteen, Monograph of the Society for Research in Child Development, National Research Council, 1937, vol. 2, no. 5.

TABLE 3.—*Effect of Mild Hyperthyroidism and Iodine on Nitrogen Balance (Subject 4, L. L.)*

Date	Nitrogen, Mg.				Date	Basal Metabolic Rate	Respiratory Quotient	Basal Calories	Weight, Pounds	Height, Inches	Medication
	Intake	Urine	Stool	Balance							
12/19–21	13.2	10.97	1.01	+1.22	12/19	+24	78	1,572	84¾	59¼	Oridine, 1 tablet (equivalent to 0.01 Gm. of iodine) daily 12/15–2/1
12/22–24	13.2	12.39	0.89	—0.08	12/21	+17	79	1,452	84¾		
12/25–27	13.2	13.38	0.90	—1.08	12/24	+14	77	1,406	84¾		
12/28–30	13.2	12.67	1.42	—0.89	12/28	+16	78	1,440	85½		
12/31–1/2	13.2	10.58	1.33	+1.29	12/31	+ 1	82	1,251	85½	59½	
1/ 3– 5	13.2	10.91	0.90	+1.39	1/ 4	+15	74	1,416	85¼		
1/ 6– 8	13.2	9.49	0.36	+3.35	1/ 7	+ 6	79	1,330	86		
1/ 9–11	13.2	12.31	0.90	—0.01	1/11	+ 7	82	1,334	87		
1/12–14	13.2	9.40	1.50	+2.30	1/14	+12	82	1,399	87		
1/15–19	13.2	11.57	1.00	+0.63	1/18	+15	83	1,435	87½		
1/20–22	13.2	9.02	1.63	+2.55	1/21	+17	78	1,483	89		
1/23–25	13.2	7.58	1.27	+4.35	1/25	+17	78	1,457	89		
1/26–28	13.2	9.23	1.33	+2.64	1/28	+16	77	1,440	88		
1/29–31	13.2	7.43	1.34	+4.43							
2/ 1– 4	13.2	10.92	1.40	+0.88	2/ 1	+12	74	1,409	88		
2/ 5– 7	13.2	9.55	1.63	+2.02	2/ 4	+ 8	73	1,364	88¼		
2/ 8–10	13.2	12.77	1.63	—1.20	2/ 8	+ 1	73	1,264	87¾	59½	
2/11–13	13.2	11.35	1.16	+1.69	2/11	— 2	80	1,219	88		
2/14–16	13.2	11.04	1.27	+1.89	2/15	+19	75	1,490	88		
2/17–19	13.2	10.67	1.53	+1.00	2/18	+15	73	1,442	87½		
2/20–22	13.2	12.15	1.27	—0.22	2/23	+12	70	1,408	88	59¾	
2/23–25	13.2	12.26	1.10	—0.16							
2/26–28	13.2	11.22	1.37	+0.61	2/26	+16	75	1,469	88½	60	
3/ 1– 4	13.2	11.82	1.13	+0.25	3/ 1	+ 9	78	1,380	88		
3/ 5– 7	13.2	10.70	1.57	+0.93							
3/ 8–10	13.2	12.23	1.17	—0.20	3/ 8	+ 9	80	1,370	87		
3/11–13	13.2	11.74	0.73	+0.73	3/11	+ 8	80	1,358	88		
3/14–16	13.2	14.32	0.77	—1.89	3/15	+ 4	78	1,308	88		
3/17–20	13.2	11.67	0.55	+0.98	3/18	± 0	80	1,250	88		
3/21–24	13.2	11.19	0.68	+1.33	3/22	+ 8	78	1,375	88	60	
3/25–27	13.2	13.14	1.20	—1.14	3/25	+19	82	1,482	86		
3/28–30	13.2	11.65	0.75	+0.80	3/29	+ 7	74	1,342	88		
3/31–4/2	13.2	12.97	0.75	—0.52	4/ 1	+ 3	80	1,312			
4/ 3– 5	13.2	9.67	1.00	+2.53	4/ 5	+ 4	77	1,325	90	60	

The diet throughout this study consisted of 2,200 calories: 82.5 Gm. of protein, 85.5 Gm. of fat and 275 Gm. of carbohydrates.

rates associated with puberty are likewise accompanied with higher retentions, which in the case reported here were not referable to an increased intake. This is borne out by a more detailed study to be reported.

Severe Hyperthyroidism.—SUBJECT 4.—E. B. (table 4) was a 14 year old girl with typical exophthalmic goiter. Her initial basal metabolic rate was + 70 per cent. After a course of iodine and rest in bed the rate fell to + 31 per cent. A nitrogen balance study carried on for two weeks prior to operation showed an average positive balance of 0.95 Gm. daily. After thyroidectomy and a fall of the rate to + 9 per cent the balance increased to +5.03 Gm. a day. The difference between the average of food calories and basal calories between the two periods was about 15 per cent; the nitrogen intake was only 2 Gm. less with the balance improved 4 Gm.

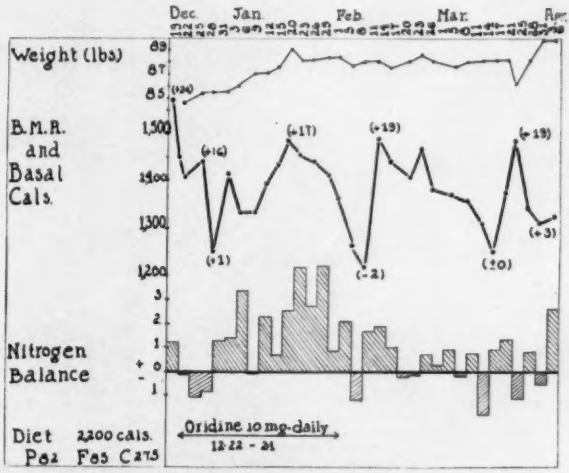


Chart 3 (L. L., pubescent with mild hyperthyroidism).—A continuous nitrogen balance study for three and one-half months, during part of which iodine was administered, at which time there is a direct parallelism between the basal metabolism and the nitrogen retention.

It might be argued that this represented evidence for a specific toxic effect since the improvement in balance seemed disproportionate to the intake and the fall in the basal metabolic rate, but it must be recalled that reserves must have been exhausted by a process severe enough to give a rate of + 70 per cent. The child had been ill four months and had lost 25 pounds (11.3 Kg.) prior to these studies, and her stores of dextrose must have been markedly depleted despite her high intake. In a study on the effect of thyroid on the utilization of dextrose, one of us [11] found a definite increase in the oxidation of this

11. Johnston, J. A.: Carbohydrate Metabolism: II. Role of the Thyroid Gland, Am. J. Dis. Child. **48**:1015 (Nov.) 1934.

TABLE 4.—*Effect of Severe Hyperthyroidism on Nitrogen Balance (Subject 3, E. B.)*

Date	Diet				Nitrogen, Mg.				Weight, Pounds	Basal Metabolic Rate	Respiratory Quotient	Total Calories
	Calories,	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Intake	Urine	Stool	Balance				
12/16	3,500	131	77.7	565.7	20.9	11.62	3.5	+5.78	87¾	+31	76	1,798
12/17	3,500	131	77.7	565.7	20.9	18.72	3.5	—1.32	87¼			
12/18						18.34	1.2		88½			
12/19						17.17	1.2					
12/20	3,072.7	109.2	121.1	386.5	17.4	16.68	1.2	—0.48	85			
12/21	1,962.0	75.2	62.0	275.8	12.0	13.65	3.0	—4.65	86			
12/22	2,763.3	113.2	98.1	357.5	18.1	15.01	3.0	+0.09	87			
12/23	3,104.9	123.7	130.1	427.5	19.7	13.97	6.1	—0.37	87			
12/24	3,242.6	114.5	114.9	437.5	18.3	14.89	6.1	—2.69	87			
12/25	3,128.7	117.2	101.1	437.5	18.7	13.58	6.1	—0.98	86¼			
12/26	3,263.7	123.2	128.1	404.5	19.4	10.16	2.7	+6.54	86	+32	80	1,819
12/27	3,143.7	115.7	128.1	382.0	18.4	10.44	2.7	+5.26	86			
12/28	3,500.0	131.0	77.7	565.7	20.9	13.40	2.7	+4.80	85			
12/29	3,719.5	138.0	147.5	460.0	22.0	18.90	3.3	—0.20	87½			
12/30	3,885.2	150.0	142.8	500.0	24.0	20.15	3.3	+0.55	86¼			
12/31	4,000.0	150.0	155.0	500.0	24.0	18.16	3.3	+2.54	87½			
1/ 1	3,938.3	150.0	148.7	520.0	24.0	23.10	3.7	—2.80	88			
1/ 2	3,882.3	145.2	153.5	480.0	23.2	19.38	3.7	+0.12	88¼	+31	78	1,798
Average	3,350	126.0						+0.76				
			Thyroidectomy 1/18									
1/24	2,875.4	105.0	110.6	365.0	16.7	9.18	1.92	+5.60				
1/25	3,000.0	112.5	116.6	375.0	18.0	8.35	1.92	+7.73		+ 9	82	1,543
1/26	3,000.0	112.5	116.6	375.0	18.0	13.62	1.92	+2.46	93¾			
1/27	3,264.0	112.5	116.6	441.0	18.0	7.89	1.54	+8.57	94½			
1/28	3,000.0	112.5	116.6	375.0	18.0	8.80	1.54	+7.66	96¼			
1/29	3,264.0	112.5	116.6	441.0	18.0	12.08	1.54	+4.38	97½			
1/30	3,000.0	112.5	116.6	375.0	18.0	10.32	3.08	+4.60	100			
1/31	3,000.0	112.5	116.6	375.0	18.0	15.78	3.08	—0.86	100¾			
2/ 1	3,050.0	111.5			18.0	10.03	3.08	+4.89		Discharged		
Average	3,050.0	111.0						+5.0				

substance so long as stores were not exhausted and with it the usual sparing effect on protein. When glycogen stores are exhausted there appears the same phenomenon as is seen in starvation—the so-called hunger diabetes, carbohydrate being stored instead of oxidized and a coincident rise in the utilization of protein occurring.

Normal Thyroid Function.—SUBJECT 5.—R. B. (chart 4 and table 5) was a child who seemed small and malnourished. At the age of 8 years and 10 months his height was 49 inches (124.5 cm.), and his weight 46 pounds (21 Kg.), with an estimated normal weight according to the Baldwin-Wood tables of 56 pounds

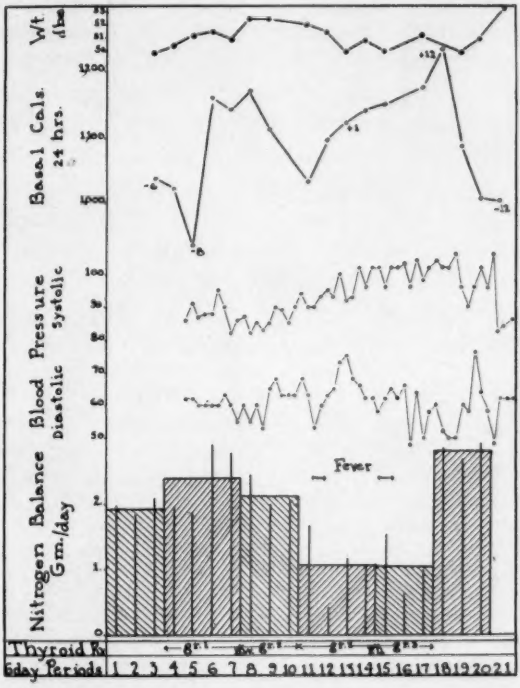

Wt. lbs.
Basal Cals. 24 hrs.
Blood Pressure Systolic
Diastolic
Nitrogen Balance Gm./day
Fever
Thyroid Rx
6day Periods
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

Chart 4 (R. B., a child with relatively normal metabolism).—Graphic representation of the effect of varying amounts of thyroid, suggesting that an anabolic effect results with small doses and a catabolic one with large doses. In this chart each single bar represents a six day balance; a cross-hatched block represents the average of all the balances contained therein.

(25.4 Kg.). The roentgenogram of the wrist showed an osseous age corresponding to the chronologic age by Todd's standards. The only item in his appraisal which raised some question as to whether he might have "masked hypothyroidism" was the dextrose tolerance test, which, after administeration of 11.5 Gm. (0.5 Gm. per kilogram) of dextrose intravenously, showed the following results: during fasting, 71 mg.; at fifteen minutes, 114 mg.; at forty-five minutes, 53 mg.; at seventy-five minutes, 57 mg., and at one hundred and fifty minutes, 63 mg. This type of "low fat" curve is found associated with thyroid defect. One grain (0.06 Gm.) daily of Burroughs, Wellcome thyroid for twenty-four days produced no

TABLE 5.—*Effect of Thyroid on R. B.*

Standard Experimental Diet 1–6 (1,900 calories) was used with administration of klim

Six Day Periods Comment	No.	1938 Dates	Nitrogen, Mg. Av. Urine	Av. Stool	Total Output	Intake	Balance	Basal Metabolic Rate	Respiratory Quotient	Calories per Square Meter per Hour	Total Calories	Weight,* Pounds	Height, Inches
	1	10/21–10/25	9.05	1.27	10.32	12.29	+1.97					46	49
	2	10/26–10/31	9.41	1.38	10.79	12.60	+1.81						
	3	11/ 1–11/ 6	9.64	1.19	10.83	12.91	+2.08	—6	0.87	48.5	1,036	49¾	49
Control Period							+1.92	Mean Balance					
Thyroid (B. W.), 1 grain daily	4	11/ 7–11/12	9.73	1.25	10.98	12.91	+1.93	—8	0.84	47.3	1,021	50½	49
started 11/8	5	11/13–11/18	9.67	1.35	11.02	12.87	+1.85	—8	0.84	47.3	935	51¼	49
	6	11/19–11/24	8.77	1.20	9.97	12.87	+2.90	—4	0.79	49.1	1,060	51½	49
	7	11/25–11/30	9.07	1.16	10.23	13.00	+2.77	—6	0.83	48.3	1,042	51	49
							+2.37	Mean Balance					
Thyroid (B. W.), 2 grains daily	8	12/ 1–12/ 6	9.07	1.22	10.29	12.72	+2.43	—5	0.82	49.0	1,070	52½	49
started 12/1	9	12/ 7–12/12	9.52	1.23	10.75	12.63	+1.88	—9	0.77	46.5	1,014	52½	49
	10	12/13–12/18	9.59	1.18	10.77	12.82	+2.05						
							+2.12	Mean Balance					
Thyroid (P. D.), 2 grains daily	11	12/19–12/24	9.71	1.21	10.92	12.59	+1.67	—9	0.76	47.3	1,032	52	49
started 12/19	12	12/25–12/30	9.44	1.50	10.94	11.34	+0.40	—2	0.80	50.6	1,093	51½	49
	13	12/31– 1/ 5	10.11	1.35	11.46	12.59	+1.13	+1	0.83	52.2	1,126	50	49
	14	1/ 6– 1/11	10.20	1.45	11.65	12.72	+1.07	+2	0.83	52.8	1,140	50¾	49
							+1.07	Mean Balance					
Thyroid (P. D.), 3 grains daily	15	1/12– 1/17	10.24	1.33	11.57	13.12	+1.55	+5	0.79	53.9	1,150	50	49
started 1/12 and discontinued	16	1/18– 1/23	10.47	1.27	11.74	12.37	+0.63						
1/29	17	1/24– 1/29	9.15	1.21	10.36	11.35	+0.99	+5	0.79	54.5	1,175	51¼	49
							+1.06	Mean Balance					
	18	1/30– 2/ 4	8.43	1.29	9.72	12.55	+2.83	+12	0.76	57.8	1,231	49½	49
	19	2/ 5– 2/10	8.57	1.09	9.66	12.33	+2.67	—2	0.82	50.4	1,077	50	49
	20	2/11– 2/16	8.21	1.00	9.21	12.12	+2.91	—9	0.85	46.6	1,006	51	49
							+2.80	Mean Balance					

* Estimated normal weight, 55 pounds (25 Kg.).

appreciable change in the total basal calories; the respiratory quotient fell slightly, and nitrogen retention definitely increased. With 2 grains (0.13 Gm.) for the next eighteen days, the basal metabolism was still unchanged; the quotient fell further, and retention was slightly less than in the previous period but still greater than the control. For the next twenty-four days, 2 grains (0.13 Gm.) of Parke, Davis thyroid was given, and then for eighteen days, 3 grains (0.19 Gm.). The metabolism now rose, and retention fell. During the final eighteen days no thyroid was given; the basal metabolic rate again fell, and retention rose.

Several points of interest arise in this study: The effects on the metabolic mixture are apparently more subtly registered than the effect on total oxidation. There is evidence of lag and a failure of these two effects to synchronize; the lowest retention occurred in the twelfth period, after forty-eight days of thyroid therapy but before the metabolic rate had changed appreciably; the second highest balance occurred in the eighteenth period, when thyroid had been discontinued but when the highest rate in the series had been attained. The effect of the small dose of thyroid was anabolic and that of the large dose catabolic. Blood pressure is recorded in the chart to bring out that while it too is taken as a measure of thyroid effect its change was not as prompt as that of the other items. In the eleventh and fifteenth periods mild infections of the upper part of the respiratory tract appeared, accompanied with a degree of fever but not enough indisposition to interfere with the taking of the full diet.

Subject 6.—R. R. (chart 5 and table 6) was a small normal boy of 6 years, who had recovered from a first infection type of tuberculosis. His study is included to illustrate the effect of small doses (½ grain [0.03 Gm.] daily of Burroughs, Wellcome thyroid) on a child who during the control period was just in balance. We feel that this fact may be a factor conditioning the difference in the reaction of this boy and that of subject R. A., the description of which follows. The average balance for twenty-eight days before thyroid was given was —0.01 mg. per day; during the sixty-six days during which he received ½ grain (0.03 Gm.) of Burroughs, Wellcome thyroid daily it was + 0.3 Gm. per day, and for the twelve days following discontinuance it was —0.27 Gm. per day. The basal metabolic rate varied between —3 and + 2 per cent. The effect here on a child just in balance of a dose small enough to increase the basal rate not beyond approximately 6 per cent was anabolic. The quotients were slightly lower with thyroid than without, as might be expected.

Subject 7.—R. A. (chart 6, table 7), a boy of 11 years, had been hospitalized for a childhood type of tuberculosis which seemed healed at the time of these observations. The bones of the wrist and hand showed an osseous age corresponding to his chronologic age by Todd's standards. The metabolic rate was somewhat low; it was felt that this was due in part to prolonged inactivity incidental to hospitalization, but whether this depression of the rate carries with it the same implications as does an actual glandular deficiency is not clear and is now being studied. During the control period of eighty days retention was high, 3.01 Gm. per day. The basal metabolic rate during this time was determined thirteen times and ranged between —16 and —5 per cent, with an average quotient of 0.85. Administration of 1 grain (0.06 Gm.) of Burroughs, Wellcome thyroid daily

TABLE 6.—*Effect of Thyroid on Nitrogen Balance of Subject 6* (R. R., Normal Boy)*

Date	Nitrogen, Mg.				Basal Metabolic Rate	Respiratory Quotient	Basal Calories	Weight, Pounds	Medication
	Intake	Urine	Stool	Balance					
1/ 4–12	9.39	7.69	1.19	+0.51	—3	82	917	43¼	None
1/18–25	9.39	8.50	1.07	—0.18					
1/27–2/6	9.39	8.22	1.42	—0.25	—2	84	930	43½	
		Average		+0.03					
2/ 7–15	9.39	8.74	1.42	—0.77					Thyroid (B. W.), ¼ grain
2/16–24	9.39	8.40	1.00	—0.01	—2	82	945		twice a day 2/7–4/12
2/25–3/6	9.39	6.66	1.16	+1.57					
3/ 7–15	9.39	7.84	1.25	+0.30					
3/16–24	9.39	8.70	1.11	—0.42	+2	81	990		
3/25–4/3	9.39	7.50	1.28	+0.61					
4/ 4–12	9.39	7.56	1.05	+0.78				44¼	
		Average		+0.30					
4/13–18	9.39	8.20	1.42	—0.23	—1	84	960		None
4/19–24	9.39	8.56	1.13	—0.30				44¾	
		Average		—0.27					

* White, aged 6 years; estimated normal weight 40 pounds (18.1 Kg.); height 42½ inches (108 cm.).
The diet throughout this study consisted of 1,400 calories.

brought the metabolic rate to normal; the quotient fell slightly, and retention decreased to 1.76 Gm. per day. Retention rose and the rate fell for twenty-four days following discontinuance.

The reason for the difference in the reaction of this boy from that of the other 2 is not clear, but it is our feeling that it was influenced by several things: 1. Our attempts [12] to influence retention by increasing the dietary nitrogen were conditioned by the state of the control balance; a definite limit to storage was evident, and when this was reached any further increase in intake was followed by the seeming

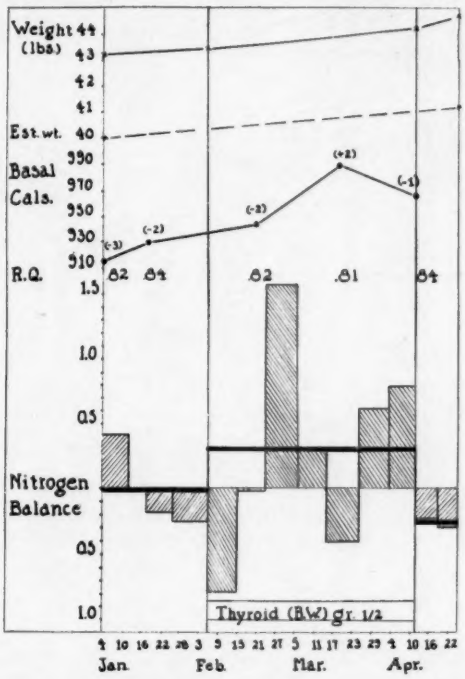


Chart 5 (R. R., a boy with normal metabolism).—Graphic representation of the effect (anabolic) of small doses. The heavy black line represents an average of all determinations within the given period. *Est. wt.* indicates estimated normal weight.

paradox of diminished retention. This difference in reaction we have noted most strikingly with extracts containing the growth hormone—large positive balances being reduced and negative balances becoming positive. 2. The change effected in the metabolic rate here was of an appreciably larger magnitude than with the other hormones; the range of the basal

12. Maroney, J. W., and Johnston, J. A.: Caloric and Protein Requirements and Basal Metabolism of Children from Four to Fourteen Years Old, Am. J. Dis. Child. **54**:29 (July) 1937.

TABLE 7.—*Studies of Nitrogen Balance* of R. A.† on Standard Experimental Diet 1-6‡*

Comment	No.	Date	Nitrogen, Mg. Intake	Nitrogen, Mg. Balance	Basal Metabolic Rate	Basal Calories	Respiratory Quotient	Weight, Pounds	Height, Inches
		1937							
	1	12/19–26	12.33	+3.95	—15	1,060	0.82	69	54¾
		1938			— 8	1,159	0.83	69½	
	2	12/27–1/4	12.98	+3.52	—12	1,104	0.80	70	
					—10	1,142	0.87	72	
	3	1/ 5–13	13.17	+3.68	— 5	1,206	0.86	71	
					—16	1,046	0.87	72	
					—12	1,130	0.84	71	
	4	1/14–22	12.95	+2.24	—15	1,090	0.95	73½	
					— 9	1,154	0.86	71½	
	5	1/23–1/31	13.20	+2.17	— 5	1,213	0.84	72¼	
					—13	1,110	0.87	72¾	
					— 9	1,159	0.83	71¾	
	6	2/ 1– 9	12.79	+2.54	—10	1,143	0.86	72	
Control period before thyroid therapy....			Average	+3.01					
Thyroid (B. W.), 1 grain daily.....	7	2/10–18	13.20	+1.77	—16	1,064	0.86	73	
					— 9	1,143	0.86	69½	
					—12	1,123	0.83	72	
Thyroid (B. W.), ½ grain daily.....	8	2/19–24 (6 day)	13.20	+1.95	— 9	1,173	0.83	72½	55
					— 8	1,167	0.79	72	
	9	2/25–3/5	13.04	+1.57	+ 1	1,309	0.81	73½	55¼
					—13	1,126	0.84	73	
Thyroid therapy discontinued.....			Average	+1.76					
	10	3/ 6–14	12.20	+1.68	—13	1,128	0.80	77½	
					—12	1,113	0.81	70¼	
					—14	1,093	0.83	71¾	
	11	3/15–23	12.92	+3.78	—14	1,098	0.78	72	
					—13	1,129	0.83	72½	
	12	3/24–29 (6 day)	13.17	+2.66	—14	1,105	0.83	72¾	
					—12	1,105	0.84	73	
After thyroid therapy			Average	+2.71					

* The nitrogen content was determined weekly from an aliquot sample of each day's diet.

† Born Jan. 11, 1926; admitted Dec. 4, 1937; weight 68½ pounds (31 Kg.); estimated normal weight 74 pounds (33.6 Kg.); height 54¾ inches (139 cm.).

‡ The diet consisted of 1,800 calories: 15 per cent protein, 35 per cent fat and 50 per cent carbohydrate.

metabolic rate was from — 16 to + 1 per cent, and in this connection it is worthy of note again that there seems to be little relation between the dose and the expected change, a fact which was strikingly illustrated by the 2 cretins.

COMMENT

The most obvious explanation of the effect of thyroid on nitrogen retention may be made in terms of the sparing effect on protein of an increase in the utilization of the other two components of the food mixture. We feel that there is definitely established an increase in the oxidation of carbohydrate as a result of thyroid stimulation;[11] this

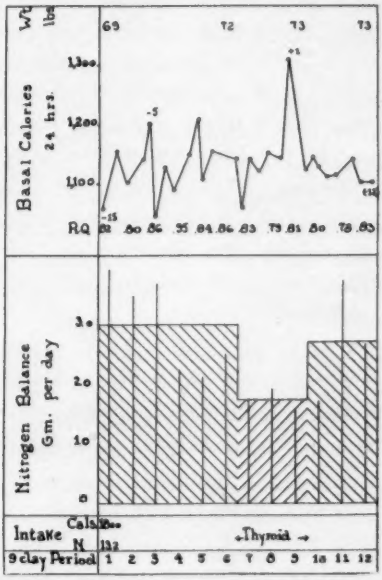


Chart 6 (R. A., a boy whose control balances were high and whose metabolism was low after prolonged hospitalization).—Graphic representation of the effect of thyroid on retention. In this chart each single bar represents a nine day balance; a cross-hatched block represents the average of all the balances contained therein.

effect is quickly obscured by the depletion of glycogen stores if large doses are used and the metabolic mixture shows a rise in the percentage of calories derived from fat—hence, toxic effects. An interesting and pertinent analogy exists in studies of the effect of salt and water on the oxidation of dextrose[13] and on the metabolism of glycogen.[14] In the

13. Johnston, J. A., and Maroney, J. W.: Carbohydrate Metabolism: III. Relation of Salt and Water to the Oxidization of Dextrose, Am. J. Dis. Child. **46**:309 (Aug.) 1933.

14. MacLeod, J. J. R.: Carbohydrate Metabolism and Insulin, New York, Longmans, Green & Company, 1926, p. 149.

case of dextrose, a slight change in p_H in the direction of acidity accelerates the oxidation, apparently by increasing the mobilization of glycogen; a further increase depresses, as a result of exhausting stores and inducing the metabolism of starvation. Dehydration induces the same phenomena, acceleration at first and depression later. The disgorgement of water following the administration of thyroid might be a factor in this. It may be, therefore, that the phenomenon is merely the secondary sparing of protein as a result of an accelerated utilization, first of carbohydrate and second of fat. When stores of these two substances are exhausted, as in prolonged hyperthyroidism, the effect is obscured by the metabolism of fasting. From this standpoint no specific anabolic effect on protein can be attributed to the administration of thyroid. However, it does not seem adequate to us to draw the merely negative conclusion that protein is not toxically acted on by thyroid; a positive effect is evident in the normal as well as in the hypothyroid child, whether this effect is secondary to an increased utilization of carbohydrate and fat or whether it does involve a primary anabolic effect on nitrogen. The striking difference in the effects of large and small doses should be stressed. Clinically, in a variety of conditions the use of thyroid "to tolerance" is much too promiscuously urged without attention to this effect, which will be even more strikingly evident in the discussion of calcium.

CONCLUSIONS

1. In the cretin the administration of thyroid is accompanied with an increase in the nitrogen balance after an initial negative phase.

2. In severely hyperthyroid children positive nitrogen balances were obtained with a high intake, but these became more strongly positive after thyroidectomy.

3. In persons with mild hyperthyroidsm, higher nitrogen balances were obtained with high than with low metabolic rates.

4. In 2 normal children, an increase in the nitrogen balance was induced with an amount of thyroid small enough to produce but a slight increase in the metabolic rate. A higher dose reversed this effect. A third apparently normal boy with a relatively high retention during the control period showed a reduction in this while receiving small amounts of thyroid, after the discontinuance of which the balance again increased.

5. The effect of thyroid in the period of growth is essentially anabolic so long as the quantity administered does not stimulate the metabolism beyond normal; this normal point is not accurately determined by oxygen consumption.

Dr. F. W. Hartman supervised the determinations of basal metabolism; Dr. O. H. Gaebler, the nitrogen analyses.

EXANTHEMA SUBITUM (ROSEOLA INFANTUM)

LOUIS H. BARENBERG, M.D.
AND
LEON GREENSPAN, M.D.
NEW YORK

Exanthema subitum (roseola infantum) is one of the mildest exanthematous diseases to which infants under 2 years are subject. It possesses, however, considerable medical interest, because its origin is unknown and because there is a good deal of confusion in differentiating it from other exanthematous diseases.

The accumulation of clinical evidence within recent years has shown that exanthema subitum is a clinical entity. The lack of information about this disease on the part of the medical profession is probably due to the fact that it is mild and is rarely encountered in hospital practice. The reports in the literature usually concern isolated cases observed in private practice. Under these circumstances the disease must have originated from manifold sources, and the reports are open to the criticism that, owing to the poorly defined onset of the disease, there is no means of knowing how long the infants were ill. Also, one is never certain whether the eruption is due to the ingestion of certain drugs or is a result of a contagious disease of which the physician failed to observe the prodromal symptoms.

It is obvious that a study of cases of this disease within the confines of a child-caring institution has marked advantages over the study of an equal number of cases in hospital or private practice. Institutional infants are observed for a considerable period within the same walls and have the same daily routine, including uniform diet and care by trained personnel, and a resident physician can observe them from the onset of the disease until they are cured. An epidemic of exanthema subitum at the Home for Hebrew Infants afforded us an opportunity for a systematic clinical and blood study.

There have been, as might be supposed, frequent outbreaks of roseola infantum at the institution. A review of the records revealed that from 1934 to 1938, inclusive, 54 cases occurred in the institution (table 1). However, the number of infants who came down with the disease in these years, exclusive of the 1938 epidemic, was not large, and blood studies were not done; hence we could not correlate the findings. The investigation to be reported, therefore, concerned itself particularly with

From the Home for Hebrew Infants, 100 West Kingsbridge Road.

the 1938 epidemic, including an accurate observation of the clinical manifestations in 27 cases and a cellular examination of the blood at the onset, during and at the end of the disease in 21 of 27. Studies of the blood were also done for 16 infants who were apparently suffering from a grippal infection when the epidemic occurred; these served as controls.

Comparatively little is known about the contagiousness of the disease. In Zahorsky's first papers on roseola infantum [1] no mention was made of the infectiousness of this disease. In subsequent writings,[2] however, he suggested the possibility of its infectious nature by the apparent immunity acquired after one attack and the increased resistance of older children to this disease. In a study somewhat comparable to ours, Cushing [3] definitely demonstrated the infectious nature of roseola infantum.

From Sept. 30 to Dec. 23, 1938, about three months, 27 infants of susceptible age came down with the disease (table 2). The incidence of infection in the respective wards varied from 35 to 45 per cent. In

TABLE 1.—*Yearly Incidence of Exanthema Subitum*

Year	No. of Cases	Year	No. of Cases
1934	6	1937	8
1935	6	1938	34
1936	0		

this respect roseola infantum ranks with scarlet fever in frequency. Apparently exanthema subitum belongs to that group of exanthematous diseases which is moderately infectious. An outbreak in a ward may affect only a certain number of infants of the susceptible age. The remainder are either protected by a natural immunity or acquire immunity after having had one attack. A few of the infants may exhibit a modified form of the disease, having an identical course and similar blood findings except for the exanthem. In these, of course, the disease goes unrecognized, as will be brought out later in this paper, unless studies of the blood are done for every infant who has an elevated temperature during an epidemic. It must be borne in mind that infants of the age period under consideration are as a rule confined to their beds, and limited opportunity is afforded for contact.

1. Zahorsky, J.: (*a*) Roseola Infantilis, Pediatrics **22**:60, 1910; (*b*) Roseola Infantum, J. A. M. A. **61**:1446 (Oct. 18) 1913.

2. Zahorsky, J., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, 1937, vol. 2, chap. 21.

3. Cushing, H. B.: An Epidemic of Roseola Infantum, Canad. M. A. J. **17**:905, 1927.

TABLE 2.—*Data on Thirty-four Cases of Exanthema Subitum in 1938*

Name	Age, Mo.	Ward	Disease		Eruption		Blood			
			Date of Onset, 1938	Duration, Days	Date of Onset, 1938	Duration, Days	Date, 1938	Leukocytes	Lymphocytes, %	Polymorphonuclears, %
V. H.	19	12	2/13	8	2/17	4	.....	.....	..	..
G. S.	38	Isol.	3/ 3	7	3/ 8	2	.....	.....	..	..
B. S.	26	11	3/30	7	4/ 4	2	.....	.....	..	..
G. T.	12	5	4/21	7	4/25	3	.....	.....	..	..
J. B.	12	8	5/27	7	5/30	4	.....	.....	..	..
N. R.	16	4	5/27	8	5/31	3	.....	.....	..	..
J. L.	14	4	9/ 1	8	9/ 7	2	.....	.....	..	..
S. T.	18	5	9/30	7	10/ 4	3	.....	.....	..	..
G. T.	18	5	10/ 7	6	10/10	3	.....	.....	..	..
D. S.	18	4	10/ 7	5	10/10	2	10/11	6,000	80	20
M. G.	15	12	10/ 8	6	10/11	3	10/11	5,000	50	48
J. P.	26	2	10/10	5	10/14	1	.....	.....	..	..
R. B.	19	12	10/13	6	10/17	2	.....	.....	..	..
M. G.	15	8	10/16	7	10/21	2	.....	.....	..	..
A. D.	15	12	10/18	7	10/22	3	.....	.....	..	..
P. G.	17	12	10/19	8	10/24	3	10/22	9,500	51	48
							10/24	4,750	80	20
							10/25	8,100	74	26
							10/26	9,000	76	24
							10/27	.....	60	40
R. R.	14	Isol.	10/19	7	10/23	3	10/22	4,500	80	20
							10/24	7,150	88	12
							10/25	6,450	84	16
							10/26	6,000	84	16
							10/28	.....	76	24
E. J.	22	12	10/23	7	10/28	2	10/26	9,000	68	32
							10/27	5,400	86	14
							10/28	5,000	88	12
							10/29	8,400	90	10
W. K.	14	12	10/23	8	10/27	4	10/26	9,000	84	16
							10/27	7,000	84	16
							10/28	7,000	88	12
							10/29	6,500	80	20
							10/31	7,600	64	36
E. A.	18	4	10/25	6	10/29	2	10/28	6,200	88	10
							10/29	6,750	81	16
							10/31	9,700	68	26
E. G.	12	Isol.	10/25	6	10/29	2	10/28	4,700	84	16
							10/29	6,000	90	10
M. G.	4	Hosp. 1	10/26	6	10/29	3	10/29	6,750	80	20
							10/31	5,900	80	20
V. B.	15	Isol.	10/28	5	11/ 1	1	11/ 1	7,650	86	14
							11/ 2	9,200	70	30
R. G.	15	10	10/30	6	11/ 3	2	11/ 1	4,475	50	50
							11/ 2	7,200	72	38
							11/ 3	5,800	76	24
							11/ 4	7,500	64	36
S. B.	16	5	10/30	8	10/ 5	2	11/ 5	5,000	80	20
							11/ 7	11,000	67	31
S. L.	12	4	10/31	5	11/ 3	2	11/ 3	6,250	76	24
							11/ 6	6,250	84	16
D. L.	18	Isol.	11/ 2	5	11/ 4	3	11/ 4	5,050	88	12
							11/ 7	5,000	88	12
J. F.	13	5	11/ 7	7	11/11	3	11/ 9	4,800	72	28
							11/12	4,450	80	20
							11/14	11,000	76	24
							11/18	.....	80	20
E. K.	14	5	11/ 8	6	11/12	2	11/12	8,650	78	22
							11/14	9,300	76	24
							11/18	10,000	70	30
L. S.	15	5	11/13	6	11/17	2	11/14	11,000	39	61
							11/15	6,000	75	25
B. P.	15	5	11/14	5	11/18	2	11/15	7,200	77	22
							11/18	7,000	82	16
A. P.	15	5	11/28	6	12/ 1	3	12/ 1	5,500	80	20
							12/ 3	9,200	92	8
							12/ 4	9,500	31	68
J. R.	16	6	12/10	8	12/16	2	12/13	18,000	20	80
							12/16	9,800	60	40
J. C.	15	7	12/23	5	12/26	2	12/24	7,050	38	60
							12/26	13,950	82	13

Most authors have emphasized the fact that roseola infantum occurs primarily among children under 2½ years of age. Fifty of our patients (93 per cent) were under 2 years. The youngest was 4 months old. There was only 1 child in this group who was older than the expected age at which exanthema subitum usually occurs; this child was 38 months old.

Glanzmann [4] in 50 cases of roseola infantum found the ratio of incidence between boys and girls as 3 to 2. In our group of cases the sex incidence was about equally divided: 26 boys and 28 girls.

Most observers have stated that the seasonal incidence is not characteristic. They have indicated, however, that most cases of roseola infantum occur during the winter and early spring, associating this syndrome with the prevalence of acute infections of the upper part of the respiratory tract. Faber and Dickey [5] reported that of 26 cases, 18 occurred between October and March; the largest number, 7 cases,

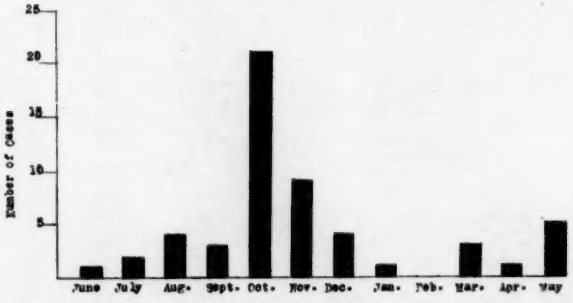


Chart 1.—Monthly incidence of exanthema subitum from 1934 to 1938.

occurred in March. We plotted our cases according to the month of the year (chart 1). We found that the greatest number of cases occurred during the fall. Winter and summer were next in prevalence. October was the outstanding month, with 21 cases.

Because more than one child of susceptible age is rarely present in a family, the incubation period of roseola infantum had never been determined until the study by Cushing in 1927.[3] In a study of 6 cases in a ward of the Montreal Foundling and Baby Hospital, Montreal, Canada, he was able to determine the period of incubation to be, on the average, ten days, with a range of eight to fourteen days. He suggested the possibility of a carrier of a different age who does not react in the same manner to the infection.

---

4. Glanzmann, E.: Das kritische Dreitagefieberexanthem der kleinen Kinder (Exanthema subitum sive criticum), Ergebn. d. inn. Med. u. Kinderh. **29**:65, 1926.

5. Faber, H. K., and Dickey, L. B.: Symptomatology of Exanthem Subitum, Arch. Pediat. **44**:491, 1927.

The epidemic under consideration was confined to a few wards located on different floors in the main building and to a ward isolated from the central building of the institution. Although the infants of the respective wards did not come in contact with each other, the nurses in charge of these wards were not restricted to one ward. This was particularly true of the night nurses, who at times did relief duty in more than one ward in the main building as well as in the isolated ward. It is therefore reasonable to assume that a nurse acted as a carrier in transmitting the disease.

We were able to trace the period of incubation for 18 children in three different wards. This was particularly definite in the isolated ward. Nine normal healthy infants were transferred to this ward, which was opened on Oct. 7, 1938. Twelve days after admission the first case of roseola infantum occurred; this was naturally considered

TABLE 3.—*Period of Incubation*

Ward 5			Ward 12			Isolation Ward		
Name	Day of Onset, 1938	Days of Incubation	Name	Day of Onset, 1938	Days of Incubation	Name	Day of Onset, 1938	Days of Incubation
S. T.*	9/30	..	M. G.*	10/ 8	..	R. R.*	10/19	..
G. T.	10/ 7	7	R. B.	10/13	5	E. G.	10/25	6
S. B.*	10/30	..	A. D.	10/18	10	V. B.	10/28	9
J. F.	11/ 7	8	P. G.	10/19	11	D. L.	11/ 2	13
E. K.	11/ 8	9	E. J.	10/23	15			
L. S.	11/13	14	W. K.	10/23	15			
B. P.*	11/14	15						
A. P.	11/28	14						

* Primary case.

as a primary case. Three secondary cases occurred at intervals of six, nine and thirteen days. Further analysis (table 3) shows that the secondary cases occurred in the other two wards within five to fifteen days. The average period of incubation was ten days. These observations are in accord with those made by Cushing.

Compared with measles, scarlet fever and other exanthematous diseases, roseola infantum is a disease of but slight importance with regard to symptoms. In the majority of cases the symptoms were not outstanding. The onset was acute in all, with a temperature between 102 and 103 F., and there was the usual picture of an acute infection of the upper part of the respiratory tract with slight coryza and congestion of the tonsillar and pharyngeal regions. In 2 infants follicular tonsillitis was associated with the onset. In 1 infant the disease was ushered in by a convulsion. In 2 others diarrhea and vomiting were the outstanding symptoms at the onset. Generally the children were comfortable, rested well and took nourishment.

Most of the writers on the subject have described a characteristic temperature for roseola infantum which is maintained for three to four days after the onset and then comes down abruptly before the appearance of the rash. Thus Park and Michael,[6] in their report of 21 cases, stated that in most cases the temperature falls by crisis and only in an occasional case by lysis. The temperature was read in all our cases every four hours during the course of the illness; thus we obtained an accurate picture of the temperature curve of each patient. Analysis of the 54 cases with regard to temperature showed that they fell into two groups. In one group of infants the temperature was elevated from the onset and then came down abruptly by crisis. In the other group the maximum temperature developed on the second day of the disease, and from then on there was a gradual descent to normal. Chart 2 represents a composite temperature curve for 27 cases in which the

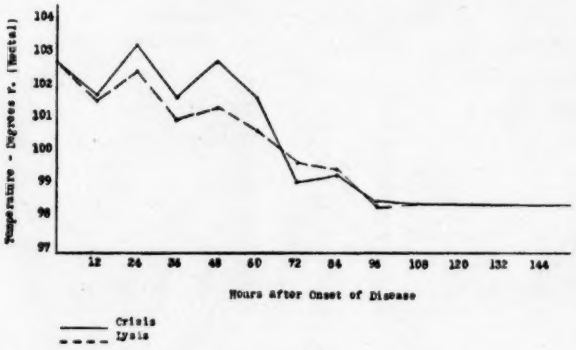


Chart 2.—Temperature curves.

temperature came down by lysis and an equal number of cases in which it came down by crisis.

A typical rubelliform rash covered the body, being most evident on the trunk, where it was discrete, and tending to become confluent on the neck. The average time of the appearance of the eruption was three and nine-tenths days after the onset of the illness. In 13 cases the rash appeared simultaneously with the fall in temperature, regardless of whether it came down by lysis or by crisis. In the remainder of the cases the eruption appeared in nine and eight-tenths hours when the temperature came down by crisis and in eleven and eight-tenths hours when the temperature came down by lysis.

According to some observers enlargement of the lymph nodes is considered a constant finding in roseola infantum. Lymphadenopathy

6. Park, J. H., Jr., and Michael, J. C.: A Peculiar Eruptive Disease Occurring in Infancy, Am. J. Dis. Child. **23**:521 (June) 1922.

was not a frequent finding in our cases. In only 8 cases was there enlargement of the glands, in 5 of the superficial cervical glands and in 3 of the occipital group. Glandular enlargement is certainly not as common in roseola infantum as it is in rubella, with which the disease may sometimes be confused.

The first study to take cognizance of the blood picture in the various stages of the disease was that of Veeder and Hempelmann [7] in 1921. They studied the blood in 8 of 20 cases in private practice and found characteristic leukopenia and relative lymphocytosis. These manifestations disappeared on the fifth day after the temperature had fallen to normal. In 1927 Faber and Dickey [5] found that the relative lymphocytosis is more constant than the reduction in the total number of white blood cells. The blood findings have been corroborated by subsequent observers.

At the beginning of the epidemic, studies of the blood were carried out in a few cases after the rash had appeared. Later, however, blood counts were done as soon as fever developed, and daily smears were laid aside for differential examination in the event the disease developed. We soon found that the premonitory leukopenia and lymphocytosis are of value in heralding that infection has taken place and the exanthem will appear at the termination of the fever.

Fifty-five white blood cell counts and fifty-eight differential counts were done, in 21 cases. A total white cell count of 6,750 and a 70 per cent lymphocyte count were taken as indicating leukopenia and lymphocytosis, respectively. In 16 cases there was leukopenia, the count ranging from 4,500 to 6,750 at some time during the course of the illness. In the other 5 cases the white cell count ranged from 7,000 to 18,000. Nineteen children showed lymphocytosis at some time during the course of the disease (table 2). As aforementioned, blood counts were done in some cases on the first day of the illness. However, it was from the third to the seventh day, inclusive, that sufficient blood studies were done to enable us to draw definite conclusions.

Analysis of the blood findings in relation to the day of the disease reveals that lymphocytosis was present in 66 per cent of the infants on the third day; it reached its maximum, affecting 100 per cent of the infants, on the fourth day, remained in 88 to 80 per cent on the fifth and sixth days and finally dropped, being present in 75 per cent of the children on the seventh day. In contrast, only 50 per cent of the children had leukopenia on the third day and 64 per cent on the fourth day. From that point on, there was a steady decline, so that on the seventh day only 25 per cent showed leukopenia (chart 3). In 6 cases the blood was studied up to the twelfth day after the onset; in 3 of

7. Veeder, B. S., and Hempelmann, T. C.: A Febrile Exanthem Ocurring in Childhood (Exanthem Subitum), J. A. M. A. **77**:1787 (Dec. 3) 1921.

these lymphocytosis persisted. No other changes were found in the blood except the presence of 6 per cent eosinophils in 1 case; this could not be explained.

Abb,[8] on the basis of a study of 4 infants with exanthema subitum during an epidemic of grip in an institution, came to the conclusions that exanthema subitum is not a disease entity but one of the manifestations of grippal infection and that the lymphocytosis which is present in exanthema subitum is also present in grip without the exanthem. During our epidemic eighteen blood and differential counts were done on 16 children who served as controls. They presented the picture which is usually considered that of grip. The blood studies, which were carried out on the third or fourth day after the onset of the infection, failed in 13 cases to show the lymphocytosis and leukopenia which in

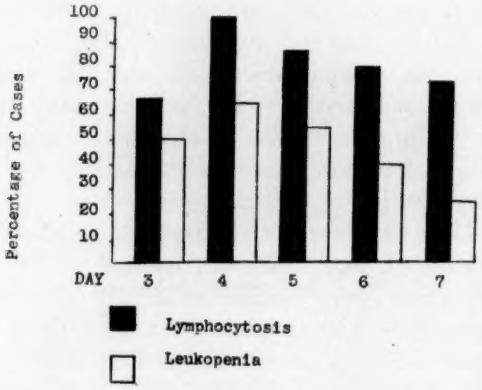


Chart 3.—Relation of lymphocytosis and leukopenia to the day of the disease.

exanthema subitum would be expected in about 100 per cent and 60 per cent of the children, respectively (table 3). The clinical course differed entirely from that of exanthema subitum, in that the temperature continued to be elevated for about six to nine days. In this connection, an experience with 1 infant is worth mentioning: R. R., 1 of the children who had roseola infantum and presented the typical blood findings, had grip at a later date. The blood at this time failed to show lymphocytosis and leukopenia.

In 3 of the 16 control cases the clinical course, with the exception of the eruption, was similar to that of exanthema subitum, the temperature falling to normal on the third or fourth day. Studies of the blood revealed a marked lymphocytosis, the concentration ranging from 70 to 87 per cent. In 1 case this persisted up to the sixth day. From

8. Abb, M.: Ist das Exanthema subitum eine selbständige Krankheit? Ztschr. f. Kinderh. **55**:339, 1933.

our observation a marked lymphocytosis associated with a typical clinical course, in the absence of the rash, may indicate an abortive or modified form of roseola infantum. It is possible that the cases of so-called grip in which Abb found lymphocytosis and leukopenia might have been cases of modified roseola without the exanthem. We believe, therefore, that during the course of an epidemic of exanthema subitum additional cases of modified disease may be disclosed if studies of the blood are made for every child in whom a sudden febrile condition develops.

Some authors have suggested that exanthema subitum is an allergic reaction which is manifested in some children in the course of an infection of the upper part of the respiratory tract, thus explaining the lack of a wide spread of the exanthem. The question of allergy

TABLE 4.—*Blood Findings for Sixteen Control Subjects*

Name	Ward	Day of Disease	Blood		
			Leukocytes	Lymphocytes, %	Polymorphonuclears, %
S. M.	Hosp. 2	4	9,500	58	42
C. R.*	1	2	16,000	53	47
		4	10,050	72	26
		5	11,000	84	16
R. M.*	1	4	10,835	87	12
M. R.*	1	4	11,000	70	30
S. G.	5	3	10,800	68	32
A. G.	5	4	18,000	60	38
H. G.	5	3	16,750	38	60
I. Z.	5	4	15,000	68	32
L. R.	5	3	9,700	44	56
B. K.	5	3	11,300	40	60
E. C.	Isol.	3	11,600	64	36
R. R.	Isol.	4	18,000	42	58
J. B.	4	4	11,200	50	48
M. F.	10	3	11,400	46	54
M. G.	12	6	11,000	62	36
A. D.	12	4	17,400	42	58

* Cases of modified exanthema subitum.

can be definitely dismissed from this study. None of the children exhibited any allergic manifestations at any time during their stay in the institution, which ranged from six months to two years. We are certain that no drug was implicated, as none of the infants received antipyretic medicaments. As mentioned before, the diet in the institution is well controlled and uniform. Moreover, studies of the blood indicated the absence of allergy. In only 1 infant was eosinophilia (6 per cent eosinophils) found. This finding is in full agreement with that of Zahorsky [2] of absence of eosinophilia in patients with roseola infantum.

Apparently roseola infantum confers a permanent immunity, and recurrences are rather rare. Zahorsky [9] cited 2 cases in which two

9. Zahorsky, J.: Roseola Infantum: Rose Rash of Infants, Arch. Pediat. 42:610, 1925.

attacks of the syndrome occurred; about 1 he was not certain. One patient in our series, G. T., had a typical syndrome in March 1938 and a similar attack six months later. Unfortunately studies of the blood were not made on either occasion.

Because of the mild character of the disease, complications are rarely associated with it. Ikeda,[10] however, found otitis media as a complication in 24 per cent of 70 reported cases. In our series of 54 cases purulent otitis media developed in only 3. It is of interest to note that in spite of the purulent infection, as a result of the otitis media there were typical lymphocytosis and leukopenia.

SUMMARY

Some of the clinical features in 54 cases of exanthema subitum (roseola infantum) are described, and studies of the blood are reported for 21 cases during an epidemic in 1938. It is pointed out that a study of this kind can be carried out only in an institution where the children are observed from the onset throughout the disease. The study corroborates the theory that this syndrome is a disease entity, and its infectiousness is emphasized. When contact was afforded to children of susceptible age, the disease assumed epidemic proportions. The incidence of infection varied from 35 to 45 per cent. We were able to trace the period of incubation in 18 cases. The average period was ten days and the range from five to fifteen days. The temperature was read every four hours during the course of the illness for every child; this brought out the fact that the eruptive stage may be preceded by either lysis or crisis, as 27 children experienced an abrupt and an equal number a gradual descent.

Fifty-five blood counts and fifty-eight differential counts for 21 children showed a high incidence of lymphocytosis and a lesser degree of leukopenia. Analysis of the blood findings in relation to the day of the disease showed that on the fourth day of the disease lymphocytosis was present in 100 per cent and leukopenia in 64 per cent of the children. The lymphocytosis persisted in some cases until the eleventh day. These blood findings associated with the clinical course were considered characteristic of the disease. Sixteen of the children who were suffering from what seemed to be a grippal infection during the epidemic of exanthema subitum served as controls. The clinical course of the disease in 13 of these differed from that of roseola infantum. Studies of the blood of these 13 children failed to show lymphocytosis. The clinical course in the remaining 3 of this group was simi-

10. Ikeda, K.: Nature of Afebrile Exanthem in Infants, with Clinical Observations, J. Pediat. (Tokyo), 1925, no. 296, p. 1.

lar to that of exanthema subitum with the exception of the exanthem. Studies of the blood revealed a marked lymphocytosis on the third and fourth days after the onset, the concentration ranging from 70 to 87 per cent. It is possible that these 3 children may have had modified exanthema subitum. This observation suggests that modified exanthema subitum may be disclosed if studies of the blood are done for every child who is suffering from a febrile condition during an epidemic of exanthema subitum.

ROLE OF ADVANCING MATERNAL AGE IN CAUSING ACHONDROPLASIA

ADRIEN BLEYER, M.D.
ST. LOUIS

Although maternal age has been abundantly sustained as a factor in the causation of mongolism,[1] of the polydactylism of guinea pigs [2] and of congenital malformations,[3] no reference has yet appeared relating to the possible role of this factor in the causation of achondroplasia.

It was hard to obtain records of maternal age at the time of birth of achondroplastic children in sufficient numbers to be worthy of study. Most of the patients who might have provided such information had been lost sight of, and, more often than not, no record of their mother's age appeared in their histories.

In the available articles on achondroplasia among the four hundred and ninety-six which appeared in the literature up to July 1938, there were reported only 47 cases in which the age of the mother was recorded or could be secured by correspondence with the author. It therefore became necessary to look elsewhere. After much hesitation and certain misgivings, it was decided to make bold and go directly to teaching centers for help. Accordingly, letters were prepared and sent to the heads of the pediatric and occasionally the orthopedic departments of many schools and hospitals in this country and Canada.

From the Pediatric Department of Washington University School of Medicine and the St. Louis Children's Hospital.

1. Jenkins, R. L.: Etiology of Mongolism, Am. J. Dis. Child. **45**:506 (March) 1933. Penrose, L. S.: The Relative Effects of Paternal and Maternal Age in Mongolism, J. Genetics **27**:219, 1933; The Relative Aetiological Importance of Birth Order and Maternal Age in Mongolism, Proc. Roy. Soc., London, s.B **115**: 431, 1934; A Method of Separating the Relative Aetiological Effects of Birth Order and Maternal Age, with Special Reference to Mongolian Imbecility, Ann. Eugenics **6**:108, 1934. Rosanoff, A. J., and Handy, L. M.: Etiology of Mongolism, with Special Reference to Its Occurrence in Twins, Am. J. Dis. Child. **48**:764 (Oct.) 1934. Bleyer, A.: The Role of Advanced Maternal Age in Causing Mongolism: A Study of 2,822 Cases, ibid. **55**:79 (Jan.) 1938.

2. Wright, S.: Effects of Age of Parents on Characteristics of the Guinea Pig, Am. Naturalist **60**:552, 1926.

3. Murphy, D. P.: Maternal Age at the Conception of the Congenitally Malformed Child: A Study Based on Six Hundred and Seven Cases, Am. J. Dis. Child. **51**:1007 (May) 1936.

Favorable responses were received from fifty-two institutions. They contributed 256 cases, bringing the group to 303. Without these added cases the study could not have gone on.

TABLE 1.—*Maternal Age in Forty-Seven Cases of Achondroplasia Reported in the Literature and in Personal Communications*

Author	Maternal Age, Years																									
	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Balme and Reid																										1
Richard Bassett								1																		
H. Baumm																			1							
Adrien Bleyer											1									1						
W. W. Brand	1					1																				
William L. Bullard											1															
Juan F. Cafferata										1																
Charon and co-workers												1														
Jules Comby										1			1				3	1								
Joseph B. Cooke										1																
V. Z. Cope																							1			
G. Durante												1			1											
Galton Laboratory									1														1			
Sidney V. Haas								1						1												
Herschen				1																						
C. P. Lapage							1																			
Frederick Langmead																1										
Lannois										1	1															
Laquiere and co-workers										1																
J. J. Leban		1																								
L. Lemaire																			1							
Alberto Muggia																1										
J. E. Pirrung																			1							
M. Plauchu													1													
Daniel L. Sexton										1	1															
Paul O. Snoke									1			1														
Masao Sumita											1															
S. A. Tchougounoff												1														
John Thompson			1																							
M. Trillat												1														
Paul Trillat												1														
Jules Voisin																	1									
J. K. Young														1												
Total	1	1	1	1	1	2		2	2	6	5	6	1	2	2	2	4	1	3	1			2			1

Dr. D. Murray Cowie, of the University of Michigan, sent 35 cases, the largest number. Dr. Edwards A. Park sent 29 from Johns Hopkins Hospital and Dr. Kenneth D. Blackfan 26 from the Children's Hospital at Harvard. Dr. P. C. Jeans sent 12 from the pediatric and orthopedic departments of the University of Iowa, and individual or several cases came from each of the remaining institutions.

TABLE 2.—*Maternal Age in Two Hundred and Fifty-Six Cases of Achondroplasia Observed in Teaching Centers and Hospitals but Not Reported in the Literature*

Source		No. of Cases	Maternal Age, Years																														
Correspondent	Institution		16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46
Dr. Mylnor Wilbur Beach	Roper Hospital, Charleston, S. C.	1	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Dr. J. Bilderback	University of Oregon, Portland, Ore.	6	..	..	..	..	1	..	..	1	1	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	2	..	..	..	..	..	..
Dr. Kenneth D. Blackfan	Children's Hosp., Harvard Med. Sch., Boston	26	1	..	1	2	2	1	..	1	1	2	2	1	1	1	1	..	1	1	1	1	1	1	1	..	1	..	..	1	..	..	..
Dr. Joseph Brennemann	Children's Memorial Hospital, Chicago	4	..	..	..	1	..	..	..	1	..	..	..	1	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Dr. Alan Brown	Hospital for Sick Children, Toronto, Canada	3	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	1	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..
Dr. Horton R. Casparis	Vanderbilt University, Nashville, Tenn.	2	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Dr. Sam W. Clausen	Strong Memorial Hospital, Rochester, N. Y.	5	..	..	..	..	..	..	..	..	..	1	..	2	..	..	..	..	1	..	..	..	1	..	..	..	..	..	..	..	..	..	..
Dr. J. V. Cooke	Washington University Dispensary, St. Louis	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	Barnes Hospital, St. Louis	4	..	..	..	..	..	..	1	1	1	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..
	St. Louis Children's Hospital, St. Louis	3	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	1	..	..	..	..
Dr. Moses Cooperstock	Northern Michigan Children's Clinic, Marquette, Mich.	3	..	..	..	..	..	..	..	..	..	..	..	..	1	..	1	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..
Dr. D. Murray Cowie	University of Michigan, Ann Arbor, Mich.	35	2	..	..	..	2	3	3	..	1	1	3	1	2	4	2	2	..	1	3	..	3	..	1	..	..	..	1	..	..	..
Dr. C. H. Crego	Shriner's Hosp. for Crippled Child., St. Louis	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Dr. Charles Davison	Montefiore Hospital for Chronic Diseases, New York	1	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Dr. W. C. Davison	Duke University, Durham, N. C.	4	..	..	..	..	..	..	..	1	..	2	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Dr. Adolph G. DeSanctis	New York Post-Graduate Medical School and Hospital, New York	4	..	..	..	..	..	..	..	1	..	..	..	..	1	1	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Dr. John C. Gittings	Hospital of the University of Pennsylvania, Philadelphia	2	..	..	..	..	..	1	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Dr. Philip Gold	Syracuse Memorial Hospital, Syracuse, N. Y.	1	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Dr. Max A. Goldstein	Central Institute for the Deaf, St. Louis	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Dr. J. E. Gonce, Jr.	Madison General Hospital, Madison, Wis.	5	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	1	1	..	..	..	..	..	..
Dr. E. J. Huenekens	Minneapolis General Hospital, Minneapolis	6	..	1	1	..	..	..	..	..	..	..	..	2	..	..	..	1	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..
Dr. Joseph B. Howland	Peter Bent Brigham Hospital, Boston	2	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..
Dr. J. C. Jaudon	St. Louis City Hospital, St. Louis	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..
Dr. P. C. Jeans	University of Iowa, Iowa City	12	..	..	..	..	..	..	..	..	2	..	1	..	1	2	1	1	..	..	2	1	1	..	..	..	..	..	..	..	..	..	..
Dr. Charles Kimball Johnson	Mary Fletcher Hospital, Burlington, Vt.	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Dr. J. A. Johnston	Henry Ford Hospital, Detroit	3	..	..	.	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	2	..	..	..	..	..	..	..	..	..	..	..	..
Dr. C. Loring Joslin	University of Maryland, Baltimore	1	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

| | | |

The basis used for comparison of the mothers' ages at the births of the achondroplastic children was the total number of living births in the Registration Area of the United States in the four years 1919, 1924, 1929 and 1934, about 7,500,000 (table 4). It was hoped that collectively the figures for these years, separated by five year intervals, might absorb in some degree the play of transitory social and economic influences. The number of births and the respective percentages for each of the seven quinquenniums of maternal age from 15 to 49 years are shown to the left of the table; corresponding numbers and percentages among the births of achondroplastic children are shown to the right.

Young women 15 to 19 years of age contribute 6.60 per cent of the births of achondroplastic children. The normal expectancy of births in this age period is 10.95 per cent. Subtracting 6.60 from 10.95 leaves 4.35 which is 39.72 per cent of 10.95. This percentage represents the degree of protection against the birth of an achondroplastic child for women of this early age in this particular group. This is the lowest point for the entire reproductive period.

In the next quinquennium, 20 to 24 years, the incidence of births of achondroplastic children rose sharply to 19.80 per cent. The normal expectancy in this period of births is 29.14. The percentage of protection against the birth of a defective child of this type has declined to 32.05.

In the quinquennium 25 to 29 years occurred 28.38 per cent of the births of the abnormal children. Since the normal expectancy for this period, 26.51 per cent, is below the percentage for births of achondroplastic children, the relatively safe period has come to an end; the figure for births of afflicted children is 7.05 per cent above the expectancy.

Women of 30 to 34 years contributed 24.09 per cent of the births of achondroplastic infants. The expectancy in the general population has now fallen to 18.20 per cent. The trend toward achondroplasia has risen to a point 32.36 per cent above the expectancy.

In the 35 to 39 year period occurred 14.19 per cent of the births of achondroplastic infants, which may be set against a norm of 11.28 per cent. The difference is 25.79 per cent of the norm; although not above the figure for the preceding quinquennium, this percentage conforms well with it.

Women of 40 to 44 years contributed 5.94 per cent of the births of achondroplastic children, against a norm of 3.52 per cent, a rise to a point 68.75 per cent above the expected figure; the group age 45

TABLE 3.—*Maternal Age in Three Hundred and Three Cases of Achondroplasia*

Maternal Age, Yr.	Cases Reported in the Literature and in Personal Communications*	Cases Observed in Institutions but not Reported in the Literature†	Total for Each Age	Total for Each Quinquennium
16	..	4	4	
17	..	3	3	
18	..	5	5	
19	1	7	8	20
20	1	8	9	
21	1	8	9	
22	1	10	11	
23	1	13	14	
24	2	15	17	60
25	..	10	10	
26	2	15	17	
27	2	14	16	
28	6	13	19	
29	5	19	24	86
30	6	14	20	
21	1	12	13	
32	2	8	10	
33	2	14	16	
34	2	12	14	73
35	4	8	12	
36	1	6	7	
37	3	8	11	
38	1	7	8	
39	..	5	5	43
40	..	8	8	
41	2	1	3	
42	..	3	3	
43	..	2	2	
44	1	1	2	18
45	..	2	2	
46	..	1	1	3

* See table 1.
† See table 2.

TABLE 4.—*Role of Advancing Maternal Age in the Causation of Achondroplasia: A Comparison of Three Hundred and Three Births of Achondroplastic Children Occurring in Seven Quinquenniums with Total Births of Living Children in the Registration Area of the United States in Similar Periods* **

7,452,483 Births in U. S. in 4 Yr.†			303 Births of Achondroplastic Children	
No. of Births	Percentage	Quinquenniums	Percentage	No. of Births
816,615	10.95	(1) 15-19 yr.	6.60	20
2,171,752	29.14	(2) 20-24 yr.	19.80	60
1,975,745	26.51	(3) 25-29 yr.	28.38	86
1,356,508	18.20	(4) 30-34 yr.	24.09	73
840,888	11.28	(5) 35-39 yr.	14.19	43
262,945	3.52	(6) 40-44 yr.	5.94	18
17,488	0.36	(7) 45-49 yr.	0.99	3

* Babies in the general population born to mothers of less than 15 years were excluded, no births of achondroplastic children having occurred under that age in this group.
† 1919, 1924, 1929 and 1934.

to 49 years contributed 0.99 per cent, as against a norm of 0.36 per cent, the advantage in favor of birth of an achondroplastic child being about 175 per cent.

The chart shows the rise in the incidence of achondroplasia with increasing maternal age in this group.

As with mongolism, the play of maternal age in cases of achondroplasia appears to start at or soon after the beginning of the reproductive period and increases steadily to its end. One may therefore conclude that the risk of bearing a child with either of these anomalies increases, if only by a little, with the passing of each menstruation.

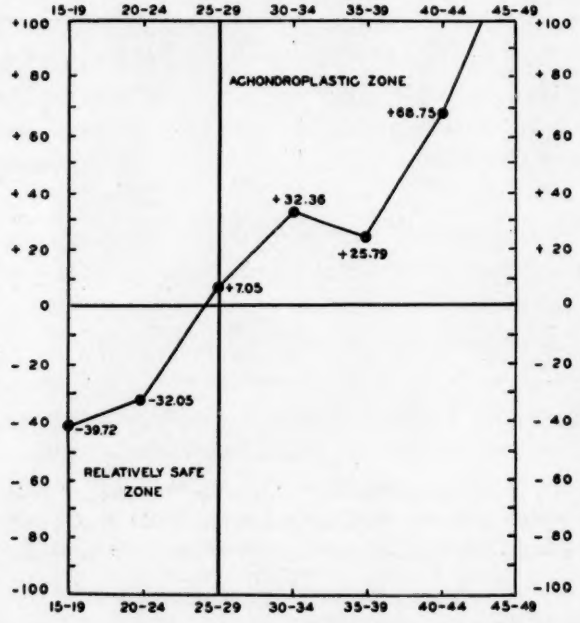


Chart showing the relation of advancing maternal age to the incidence of achondroplasia in the 303 cases of the study. The vertical columns of figures represent percentages of incidence and the horizontal columns quinquenniums of maternal age.

"Advancing" rather than "advanced" maternal age is the term to be preferred in designating this factor.

Whether in these situations maternal age is in itself a cause of the defects or whether it is coincidental with another factor, as yet undetermined, is of course unknown.

819 University Club Building.

OBESITY IN CHILDHOOD

II. BASAL METABOLISM AND SERUM CHOLESTEROL OF OBESE CHILDREN

HILDE BRUCH, M.D.
NEW YORK

Determinations of basal metabolism are widely used in the clinical study of obese patients, apparently in the expectation of arriving at some understanding of the underlying disturbance. Von Noorden [1] classified obesity as exogenous and endogenous and defined endogenous obesity as characterized by a lowered metabolism or, as he called it, "Verlangsamung der Zersetzungsenergie der Zellen." He stated that obesity of the endogenous type is rare. Since hypofunction of the thyroid gland is associated with a depression of the basal metabolism, the conclusion is frequently drawn that a low basal metabolic rate in an obese person is indicative of hypothyroidism.

The term basal metabolic rate is ambiguous, and its inconsistent use has caused much confusion. Many authors designate by basal metabolic rate the percentage deviation of the observed value from some normal standard. The most widely accepted standard uses surface area as the unit of comparison. In numerous clinical papers in which the diagnosis "obesity of primary or secondary hypothyroid origin" is based on the observation of a low basal metabolic rate, inadequate information is given as to the method of computation. Workers who have critically evaluated the significance of standards for the result have not recorded a lowered metabolic rate or even found an elevation corresponding to the excess in weight.[2]

In dealing with growing children, who are constantly changing subjects, the interpretation of metabolic tests is even more difficult. The

---

This investigation has been aided by a grant from the Josiah Macy Jr. Foundation.

From the Department of Pediatrics, College of Physicians and Surgeons, Columbia University, the Pediatric Division of the Vanderbilt Clinic and the Babies Hospital.

1. von Noorden, C.: Die Fettsucht, ed. 2, Vienna, Alfred Hölder, 1910.

2. *(a)* Lauter, S.: Zur Genese der Fettsucht, Deutsches Arch. f. klin. Med. **150**:315, 1926. *(b)* Strang, J. M., and Evans, F. A.: The Energy Exchange in Obesity, J. Clin. Investigation **6**:277, 1928. *(c)* Short, J. J., and Johnson, H. J.: The Increased Metabolism of Obesity, J. A. M. A. **106**:1776 (May 23) 1936.

extensive work of Talbot and his associates [3] has shown that surface area standards, which give accurate information for the adult, are not satisfactory for children; they have based one set of standards on body weight. Since height is less subject to rapid change than weight, they have advocated also the use of height standards. The figures for heat production used in the calculation of their height standard were obtained from children whose weight was average for their height; therefore, this standard can be called the standard for the "expected weight." Some of the differences in the results of different workers [4] may be explained by geographic factors, as Talbot and his associates pointed out. On the whole, the problem of heat production in normal growing children has been adequately handled. No satisfactory method has been found, however, of interpreting the findings for children of abnormal bodily dimensions, such as obese children.

The basal metabolism of obese children has been observed by various workers, but only a few have given adequate information as to the method of calculating their results. Topper and Mulier [5] used standards which do not take body weight into consideration. They related their results for 70 children 6 to 14 years of age and 13 to 75 per cent overweight to Pirquet's standards for sitting height and to Talbot's prediction for height, and reported usually a normal basal metabolism with a tendency toward high normal. They assumed that part of the increase may be accounted for on the basis of constant overfeeding. Talbot and his co-workers [3] reported findings for 24 girls 1 to 15 years old and on the average 47 per cent overweight and reviewed some of the previously reported data. They found "little change in the average figures when calories are referred to weight and an increasing difference with increasing obesity when referred to height." This seems to indicate that the weight standard gives a more accurate picture than the height standard and that there is an increase in active heat-producing tissue with increasing weight. Talbot and his associates warned, however, that from the clinical point of view the problem is by no means solved and that further study of this complicated subject is needed. In a recent contribution, de Bruin [6] reported his observations on 13 boys and 22 girls 2¾ to 13 years old and 20 to 57 per cent overweight. He proposed the use of a

3. Talbot, F. B.; Wilson, E. B., and Worcester, J.: Basal Metabolism of Girls: Physiologic Background and Application of Standards, Am. J. Dis. Child. **53**:273 (Jan., pt. 2) 1937.

4. Lewis, R. C.; Kinsman, G. M., and Iliff, A.: The Basal Metabolism of Normal Boys and Girls from Two to Twelve Years Old, Inclusive, Am. J. Dis. Child. **53**:348 (Jan., pt. 2) 1937.

5. Topper, A., and Mulier, H.: Basal Metabolism of Children of Abnormal Body Weight: I. Basal Metabolism of Overweight Children, J. A. M. A. **92**: 1903 (June 8) 1929.

6. de Bruin, M.: Basal Metabolic Rate in Children with Abnormal Bodily Dimensions, Am. J. Dis. Child. **57**:29 (Jan.) 1939.

new standard for obese children and suggested "the standard for weight for the actual height increased by one third of the excess weight over the standard weight." This correction was arrived at empirically; it is offered as an expression of the metabolic activity of the excess fat tissue, which, though less active than normal tissue, nevertheless cannot be considered completely inactive. No attempt was made to interpret the findings in terms of pathologic deviation or dysfunction of the endocrine glands.

In contrast to these reserved presentations, publications dealing with the clinical aspects of obesity have used the finding of a "low" basal metabolic rate more or less uncritically as an expression of hypothyroidism. In order to demonstrate whether or not some of these seemingly low basal metabolic rates might be justly interpreted as manifestations of hypothyroidism, the study of the serum cholesterol level in the same group of patients appears indicated. Numerous studies of the relation between thyroid activity, the basal metabolic rate and the values of serum cholesterol have been reported during the last two decades.[7] Discrepancies in the results obtained by various authors can be explained to a great extent by differences in technic. Cutting, Rytand and Tainter [8] showed by statistical analysis of their own findings and those in previously published reports that a "significant, inverse, curvilinear correlation" exists between serum cholesterol and basal metabolism, provided that the changes in the metabolism are due to thyroid activity. In conditions other than thyroid disease no consistent relation between the basal metabolic rate and the concentration of blood lipds has been found. In congenital [9] as well as operative [10] myxedema and in cases of mild

7. *(a)* Epstein, A. A., and Lande, H.: Studies on Blood Lipoids: The Relation of Cholesterol and Protein Deficiency to Basal Metabolism, Arch. Int. Med. **30**:563 (Nov.) 1922. *(b)* Hurxthal, L. M.: Blood Cholesterol in Thyroid Disease: Effect of Treatment, ibid. **52**:86 (July) 1933. *(c)* Mason, R. L.; Hunt, H. M., and Hurxthal, L.: Blood Cholesterol Values in Hyperthyroidism and Hypothyroidism: Their Significance, New England J. Med. **203**:1273, 1930.

8. Cutting, W. C.; Rytand, D. A., and Tainter, M. L.: Relationship Between Blood Cholesterol and Increased Metabolism from Dinitrophenol and Thyroid, J. Clin. Investigation **13**:547, 1934.

9. *(a)* Bronstein, I. P.: Studies in Cretinism and Hypothyroidism in Childhood: I. Blood Cholesterol, J. A. M. A. **100**:1661 (May 27) 1933. *(b)* Schwarz, H., and Topper, A.: Cholesterol Partitions of the Blood in Myxedema (Cretinism), J. Pediat. **3**:242, 1933. *(c)* Hess, J. H.: Blood Cholesterol and Creatine Excretion in the Urine as Aids to Diagnosis and Treatment of Hypothyroidism, Ann. Int. Med. **8**:607, 1935.

10. *(a)* Gilligan, D. R.; Volk, M. C.; Davis, D., and Blumgart, H. L.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: Relationship Between Serum Cholesterol Values, Basal Metabolic Rate and Clinical Aspects of Hypothyroidism, Arch. Int. Med. **54**:746 (Nov.) 1934. *(b)* Schnitker, M. T.; Van Raalte, L. H., and Cutler, E. C.: Effect of

(Footnote continued on next page)

hypothyroidism [11] hypercholesteremia is found regularly as a manifestation of hypothyroidism, a clinical observation which has been confirmed by animal experiments.[12]

Results of studies of the serum cholesterol of obese patients have been less uniform. Bruger and Poindexter,[13] reviewing the older literature on the subject, drew attention to the fact that in most publications no clear differentiation has been made between the state of obesity and complicating degenerative diseases. Their own observations of 94 adult patients led to the conclusion that uncomplicated obesity is not associated with a rise in serum cholesterol. These authors reported also that the cholesterol content of the plasma in uncomplicated obesity is not altered primarily by reduction in weight with a low caloric diet. Little work has been done on obese children. White and Hunt [14] studied the blood cholesterol of diabetic children and observed a high value following overnutrition and increase in weight; subnormal weight also was associated with an increase in blood cholesterol. Molitch and Poliakoff [15] determined the cholesterol level of 505 boys with and without endocrine dysfunction, including a few boys with "adiposogenitalism." No significant deviation from the normal group was observed, nor any correlation between total serum cholesterol, basal metabolism and the mental level. Briskas [16] reported on the examination of the blood cholesterol of 117 obese children. Twenty-two of these subjects were described as suffer-

---

Total Thyroidectomy in Man: Laboratory Studies and Observations of Clinical Effects in Thirty-Nine Cases, ibid. **57**:857 (May) 1936. (*c*) Langmann, A. G., and Bruch, H.: Carcinoma of the Thyroid Gland in Children: Report of a Case Associated with Multiple Anomalies of Development, with Studies of Basal Metabolism, Serum Cholesterol and Creatine Excretion After Thyroidectomy, Am. J. Dis. Child. **56**:616 (Sept.) 1938.

11. Boyd, E. M., and Connell, W. F.: Plasma Lipids in the Diagnosis of Mild Hypothyroidism, Quart. J. Med. **6**:467, 1937.

12. *(a)* Turner, K. B.; Present, C. H., and Bidwell, E. H.: The Role of the Thyroid in the Regulation of the Blood Cholesterol of Rabbits, J. Exper. Med. **67**:111, 1938. *(b)* Schmidt, L. H., and Hughes, H. B.: The Free and Total Cholesterol Content of Whole Blood and Plasma as Related to Experimental Variations in Thyroid Activity, Endocrinology **22**:474, 1938.

13. *(a)* Bruger, M., and Poindexter, C. A.: Relation of the Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases (Diabetes Mellitus, Essential Hypertension, Osteo-Arthritis and Arteriosclerosis), Arch. Int. Med. **53**:423 (March) 1934. *(b)* Poindexter, C. A., and Bruger, M.: Effect of Low Caloric Diets and Resultant Loss in Weight on Plasma Cholesterol in the Obese, ibid. **56**:884 (Nov.) 1935.

14. White, P., and Hunt, H.: Cholesterol of the Blood of Diabetic Children, New England J. Med. **202**:607, 1930.

15. Molitch, M., and Poliakoff, S.: Cholesterol Metabolism in Children With and Without Endocrine Dysfunction, Arch. Pediat. **53**:613, 1936.

16. Briskas, S. B.: Les obésités chez l'enfant (à propos de 117 observations), Progrès méd., Jan. 16, 1937, p. 90.

ing from hypothyroidism, with obvious clinical manifestations of the condition, such as mental retardation, dry rough skin, dry hair and disturbance of osseous and genital development. In these 22 the cholesterol level was markedly higher (100 per cent and more) than in the normal series. After thyroid treatment, a drop in the cholesterol was observed. In all other cases, which he described as instances of simple obesity, no deviation from the normal was noted.

This paper will be concerned with an attempt to appraise the clinical usefulness of estimations of basal metabolism of obese children. The previously reported observation of accelerated growth and development of obese children [17] has raised considerable doubt as to whether any connection exists between obesity and hypofunction of the thyroid gland. Determinations of serum cholesterol have been made and will be examined for their value in differentiating between obesity due to hypothyroidism and obesity in which there is no evidence of thyroid disease.

DESCRIPTION OF THE GROUP STUDIED

This report is based on the study of 47 boys and 49 girls 2 to 14 years old and 20 to 108 per cent overweight. The degree of obesity has been expressed as the percentage difference between the observed weight and the expected weight for height and age, according to the Baldwin-Wood [18] tables. The boys were on the average 43.9 per cent overweight and the girls 46.2 per cent.

A detailed description of the group under investigation has been given in the previous communication.[17] Fourteen children, 5 boys and 9 girls, have been added since those figures were compiled, while other children are not included in the present study since the laboratory measurements were not carried out. The composition of the group reported in this paper did not show any significant difference from that previously described with regard to degree of obesity, racial background, age distribution, physical growth and development and mental status. The pertinent data are presented in tables 1 and 2, in which the children are arranged according to age at the time the examinations were made. Patients who were not mentioned in the previous paper are designated by an asterisk. The others can be easily identified from their position and initials. Differences in age and degree of obesity find an explanation in the fact that after the first visit to the clinic sometimes months or even years elapsed before the patient reappeared for examination. It was generally considered not advisable to order laboratory examinations at the time of the first visit.

ACCUMULATION OF DATA

The determinations of basal metabolism were carried out in the basal metabolism department of the Presbyterian Hospital. Each patient received standardized written instructions as to previous rest, omission of breakfast and transportation to the hospital. After arrival, before the test was performed, the patients rested for thirty to sixty minutes, or longer when they appeared not fully relaxed.

17. Bruch, H.: Obesity in Childhood: I. Physical Growth and Development of Obese Children, Am. J. Dis. Child. **58**:457 (Sept.) 1939.

18. Baldwin, B. T., and Wood, T. D.: Weight-Height-Age Tables, New York, American Child Health Association, 1920.

The Benedict-Roth apparatus,[19] which measures the oxygen consumption and from this permits one to estimate the production of calories, was used. Several tests, at least two, of six minutes' duration were obtained. A minimum agreement of 4 mm. between the oxygen consumption lines of different determinations was

TABLE 1.—*Classification of Obese Boys*

						Basal Metabolic Rate					
		Age		Over-weight, Per-centage	Calories per 24 Hr.	Talbot Height Stan-dard	Talbot Weight Stan-dard	Differ-ence (Height Minus Weight)	Du Bois Surface Area Stan-dard	Cholesterol	
No.	Initials	Yr.	Mo.							Mg. per 100 Cc.	Ratio
1	H. D.	2	4	66	.....	....	....	..	....	233.5	2.49
2	S. G.	2	6	28	.....	....	....	..	....	222.8	2.60
3	C. C.	3	8	41	.....	....	....	..	....	237.3	2.47
4	T. A.	5	4	37	.....	....	....	..	....	122.8	2.27
5	P. R.	5	7	66	964	+ 6	—26	32	—26	155.5	2.96
6	H. B.	5	10	54	1,082	+16	— 9	25	—14	301.3	2.68
7	M. N.	6	2	30	1,135	+11	— 6	17	—14	213.3	2.66
8	R. Y.	6	7	32	.....	....	....	..	....	194.5	2.88
9	L. R.	6	8	24	1,238	+24	+ 8	16	— 4	218.0	2.41
10*	L. B.	6	8	30	1,310	+32	+12	20	+ 2	165.0	2.28
11	J. O'C.	6	11	43	1,242	+21	— 8	29	—15	108.0	2.66
12*	J. D.	7	1	60	.....	....	....	..	....	183.3	2.57
13	W. G.	7	3	25	1,155	+ 1	— 9	10	— 9	204.5	2.44
14	W. O'G.	7	5	53	1,222	+20	—10	30	—16	165.8	3.00
15	H. G.	7	7	54	1,265	+30	0	30	— 4	196.5	2.67
16	H. M.	7	10	54	1,182	+ 7	—13	20	—21	.....	....
17	A. L.	8	3	43	1,392	+22	0	22	—12	135.5	2.27
18	S. G.	8	6	49	.....	....	....	..	....	199.0	3.30
19	S. S.	8	11	29	1,310	+22	0	22	— 7	.....	....
		12	8	39	.....	....	....	..	....	159.6	2.49
20	M. S.	9	..	35	1,075	— 9	—24	15	—34	160.3	2.43
21	N. S.	9	1	27	.....	....	....	..	....	207.0	2.61
22	R. P.	9	4	26	.....	....	....	..	....	223.6	2.28
23	S. F.	9	8	37	1,132	— 9	—22	13	—32	220.3	2.42
24	F. B.	9	9	37	1,290	+13	— 7	20	—16	282.0	2.40
25*	D. B.	9	9	59	1,235	+16	—11	27	—16	280.6	2.64
26	J. N.	9	11	30	1,590	+30	+16	14	+ 4	177.0	2.82
27	B. C.	10	..	30	.....	....	....	..	....	225.0	2.91
28	S. L.	10	2	19	1,490	+10	+ 2	8	—13	222.5	2.90
29*	H. P.	10	6	79	1,452	+22	— 9	31	—16	197.8	3.36
30	S. A.	10	6	47	1,400	+ 3	—15	18	—22	159.0	2.49
31	H. L.	10	9	70	1,755	+46	+12	34	+ 5	230.0	2.57
32	R. v. A.	10	10	47	1,272	+ 8	—11	19	—19	250.0	2.52
33	B. F.	11	..	78	1,850	+44	+ 4	40	— 3	183.8	2.48
34	G. T.	11	9	86	1,470	+17	—16	33	—21	284.0	3.09
35	S. T.	11	9	29	1,590	0	— 5	5	—18	193.8	2.32
36*	A. W.	11	11	48	.....	....	....	..	....	187.8	2.27
37	P. Z.	12	..	39	1,432	+ 5	— 9	14	—17	212.3	2.69
38	J. P.	12	1	48	1,555	+20	— 3	23	+12	160.5	3.03
39	H. P.	12	4	39	1,268	+ 8	—11	19	—18	250.0	2.68
40	M. M.	12	4	31	1,608	+16	+ 4	12	— 9	210.0	2.47
41	J. G.	12	5	90	1,825	+36	— 4	40	— 9	227.8	2.56
42	S. Sh.	12	6	32	1,370	+ 6	—10	16	—18	235.3	2.50
43	D. F.	12	7	54	1,825	+23	+ 2	21	— 7	.....	....
		14	7	57	.....	....	....	..	....	223.8	2.67
44	S. R.	12	10	40	1,538	+19	— 2	21	— 9	192.5	2.44
45	L. R.	13	1	52	.....	....	....	..	....	212.0	2.31
46	E. P.	13	2	91	1,632	+30	— 8	38	—10	243.0	2.47
47	N. F.	13	6	23	1,225	— 9	—18	9	—26	177.8	2.39

* Patient not mentioned in previous paper.

required; if this agreement could not be achieved the results were discarded and the patient was requested to come for reexamination on some other day.

I am aware that metabolic work on patients who are not under strictly controlled conditions is open to criticism. Du Bois[20] estimated that results obtained

19. Warren E. Collins, Inc., Boston, manufacturer.

20. Du Bois, E. F.: Basal Metabolism in Health and Disease, ed. 3, Philadelphia, Lea & Febiger, 1936.

on trained subjects, sleeping in the laboratory, fall on an average about 5 per cent below those obtained on untrained subjects.

The aim of this study was the clinical evaluation of determinations of basal metabolism carried out under conditions which can be duplicated in any laboratory

TABLE 2.—*Classification of Obese Girls*

						Basal Metabolic Rate					
		Age		Over-weight, Per-centage	Calories per 24 Hr.	Talbot Height Stan-dard	Talbot Weight Stan-dard	Differ-ence (Height Minus Weight)	Du Bois Surface Area Stan-dard	Cholesterol	
No.	Initials	Yr.	Mo.							Mg. per 100 Cc.	Ratio
1	A. Y.	2	..	68	.....	....	....	..	....	182.5	2.55
2	S. B.	2	9	45	.....	....	....	..	....	173.3	2.45
3	M. S.	3	6	41	.....	....	....	..	....	215.5	2.57
4	M. E.	5	1	30	860	+ 4	— 9	13	—19	.....	....
5*	Z. F.	5	7	74	843	+ 3	—24	27	—26	168.4	2.06
6	M. B.	5	9	60	740	0	—36	36	—23	168.0	2.36
7	F. P.	6	1	62	1,074	+12	—17	29	—19	217.0	2.47
8	S. R.	6	7	29	985	+ 2	— 8	10	—21	192.0	2.52
9*	H. W.	6	8	34	.....	....	....	..	....	196.6	2.52
10	B. T.	6	9	52	1,058	+12	—10	22	—18	212.0	3.03
11	G. B.	6	10	108	1,478	+52	+ 6	46	— 2	159.0	2.47
12	G. F.	7	..	53	1,104	+16	— 8	24	—17	168.8	2.47
13	A. C.	7	1	49	1,400	+37	+11	26	— 2	182.0	2.74
14	E. B.	7	6	50	1,230	+18	— 5	23	—14	163.3	2.51
15	T. S.	7	10	50	1,235	+ 9	— 7	16	—18	264.5	2.67
16	M. B.	8	1	31	1,188	+23	+ 5	18	— 2	206.3	2.57
17	Y. M.	8	5	50	1,360	+22	— 2	20	—18	.....	....
18	A. S.	8	6	38	1,175	+27	+ 8	21	+ 1	231.0	2 67
19*	S. L.	8	6	34	.....	....	....	..	....	207.8	2.88
20	G. G.	8	7	41	1,110	+12	— 8	20	—14	168.3	2 83
21	A. E.	8	8	20	.....	....	....	..	....	209.5	2.18
22	M. Z.	8	10	81	1,345	+30	+ 2	28	— 4	283.0	2.73
23	C. P.	8	10	36	1,300	+16	+ 2	14	— 8	176.8	2.55
24*	M. S.	8	11	54	1,220	+25	0	25	—11	206.5	2.73
25	E. C.	9	..	76	1,278	+ 5	—18	23	—25	.....	....
26	C. B.	9	..	42	1,110	+11	— 8	19	—17	228.5	2.27
27*	K. F.	9	1	53	.....	....	....	..	....	190.0	2.48
28	B. G.	9	2	23	1,285	+25	+ 7	18	— 1	.....	....
29	A. McL.	9	5	25	1,425	+17	+ 8	11	— 7	247.5	2.80
30	S. G.	9	6	20	1,258	+ 6	0	6	—10	.....	....
31	A. B.	9	6	41	1,410	+27	+ 8	21	— 2	.....	....
32	G. M.	9	7	46	1,332	+14	+ 1	13	— 9	155.5	2.88
33*	J. F.	9	7	64	1,452	+39	+ 9	30	+ 1	185.4	2.46
34	A. C.	10	1	50	.....	....	....	..	....	175.8	3.03
35	R. W.	10	4	49	1,330	+ 3	— 5	8	—14	277.3	2.67
36	R. L.	10	5	34	1,392	+ 2	— 5	7	—17	214.0	2.72
37	M. M.	10	7	25	1,705	+18	+13	5	— 1	181.5	2 53
38	L. S.	10	10	55	2,000	+35	+12	23	+ 6	185.8	2.61
39*	C. B.	11	..	37	.....	....	....	..	....	154.8	2.51
40*	R. C.	11	3	35	.....	....	....	..	....	247.5	2.54
41	R. K.	11	4	41	1,350	+13	— 3	16	—10	192.5	2.75
42	M. H.	11	7	26	1,284	+ 3	— 6	9	—21	192.0	2.12
43	J. A.	11	8	32	.....	....	....	..	....	135.5	2.65
44	J. F.	11	9	52	1,388	+10	— 9	19	—14	178.3	2.89
45	H. S.	11	10	37	1,255	— 4	—10	6	—17	184.5	2.47
46	F. R.	11	10	41	1,314	0	—12	12	—17	174.3	2.60
47*	D. K.	12	6	47	.....	....	....	..	....	168.4	2.46
48	I. V.	13	4	100	1,730	+33	—11	44	— 7	173.3	2.89
49	L. N.	14	1	22	1,242	—16	—17	1	—22	190.0	2.74

* Patient not mentioned in previous paper.

conducted with reasonable care. It is on such determinations that the clinical diagnoses are based and not on tests carried out under the exacting conditions of a laboratory experiment.

Cholesterol determinations were made on samples of blood obtained at the time of a visit to the clinic—that is, at different times of the day and without

regard to previous intakes of food. All determinations were done on blood serum. The method of Schoenheimer and Sperry [21] was used; the majority of the analyses were performed by Dr. W. M. Sperry.

Determinations of basal metabolism and of cholesterol which are presented as simultaneous were carried out generally within a week of each other. No medication—specifically no endocrine product—which might have influenced the results was given during the interval.

BASAL METABOLISM

In this paper, the term basal metabolism or total basal metabolism is used to denote the number of calories produced in twenty-four hours

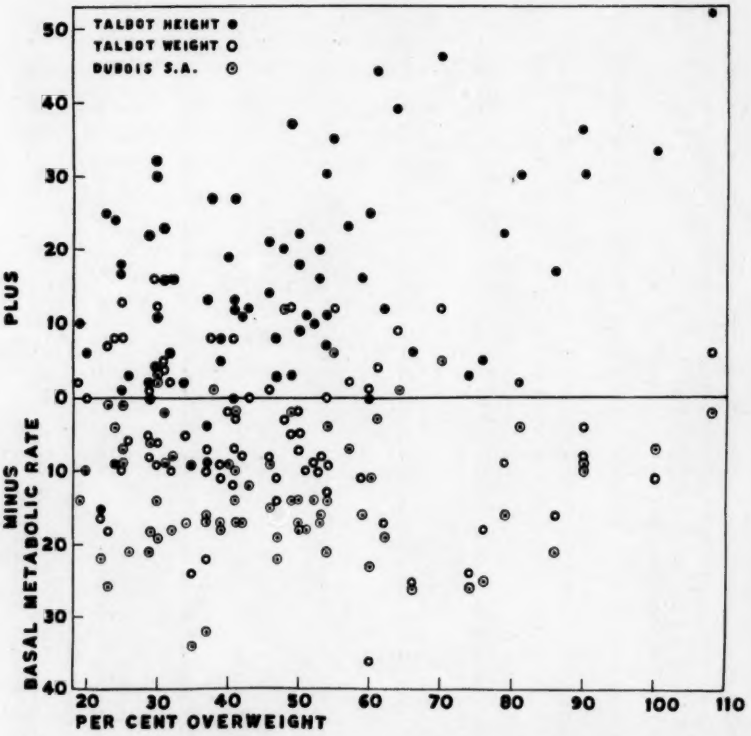


Chart 1.—Basal metabolic rates computed from different standards arranged according to degree of obesity. The solid dots indicate calculations from Talbot's height standards, the empty circles the values from Talbot's weight standards and the circles with a central dot the values from surface area standards (Du Bois standards modified by Boothby and Sandiford).

under standard conditions. Basal metabolic rate indicates the percentage deviation of this value from a standard value relating to some unit of body measurement.

21. Schoenheimer, R., and Sperry, W. M.: A Micromethod for the Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**:745, 1934.

The results of the determinations, which were done on 35 boys and 37 girls, are recorded in tables 1 and 2 as calories per twenty-four hours. The basal metabolic rates have been calculated on the basis of the standards for standing height and body weight prepared by Talbot [22] and for surface area by Boothby and Sandiford.[23] The latter standard, which represents a modification of that of Du Bois,[20] is widely used in clinical laboratories, since the instructions as to the computation accompany the Benedict-Roth apparatus.

The basal metabolic rates calculated by these different standards are presented in relation to the severity of the obesity in chart 1, in which each test is represented by three different marks. The wide discrepancies in the results are obvious; the values for standing height diverge more and more from the calculations for weight and surface area with increasing severity of the condition. The calculation for surface area tends to give the lowest basal metabolic rate. The use of body weight standards

TABLE 3.—*Basal Metabolic Rates of Seventy-Two Obese Boys and Girls*

Rates Calculated in Percentage	Talbot Height Standard	Talbot Weight Standard	Du Bois Surface Area Standard
Above +30	9 (12.5)	.....	.....
+10 to +30	36 (50)	6 (8.4)	1 (1.4)
0 to +10	22 (30.6)	20 (28)	6 (8.3)
0 to —10	4 (5.5)	29 (40.2)	23 (32)
—10 to —30	1 (1.4)	16 (22)	40 (55.6)
Below —30	.....	1 (1.4)	2 (2.7)

The figures in parentheses indicate the percentage of the total number of cases and add up to 100 in each column.

brings a result closer to the zero line, which indicates the normal rate. The majority of the figures calculated from the predictions based on height are above normal. The distribution of the different basal metabolic rates above and below normal is presented in table 3. If ± 10 per cent is considered the normal range, 36.1 per cent of the values based on height, 68.2 per cent of the calculations based on weight and 40.3 per cent of rates related to surface area fall within this range. The rest of the values based on height, with 1 exception, are above the normal range, while the remaining figures based on surface area fall below. The averages for the three calculations are: for boys, — 12.9 per cent on the basis of surface area, — 5.8 per cent on the basis of body weight and + 15.9 per cent on the basis of standing height, and for girls, — 11.8 per cent, — 3.94 per cent and + 15.3 per cent, respectively.

22. Talbot, F. B.: Basal Metabolism Standards for Children, Am. J. Dis. Child. **55**:455 (March) 1938.

23. Boothby, W. M., and Sandiford, I.: Normal Values of Basal or Standard Metabolism: A Modification of the Du Bois Standards, Am. J. Physiol. **90**:290, 1929.

The growth with increasing obesity of the difference between basal metabolic rates obtained by height and by weight standards suggests that this difference is a function of the weight excess. The correlation coefficient between these two factors was calculated as 0.896 for boys

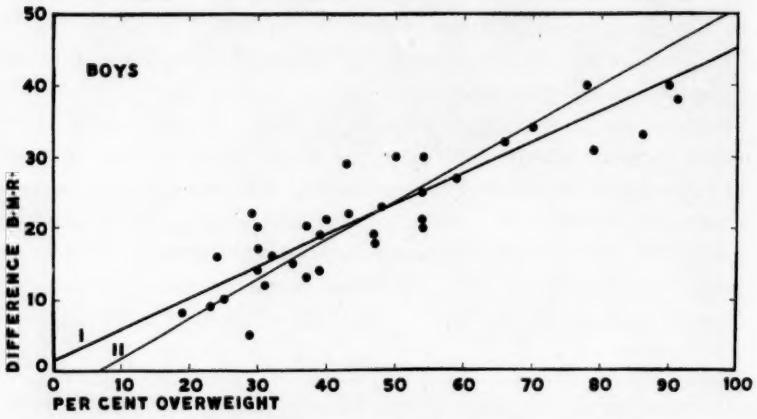


Chart 2.—Relation between excess in weight of boys and difference in basal metabolic rates computed from Talbot's height and weight standards. Line I indicates the prediction equation for difference in basal metabolism rates from excess weight. Line II represents the prediction of weight excess from the difference in basal metabolic rates.

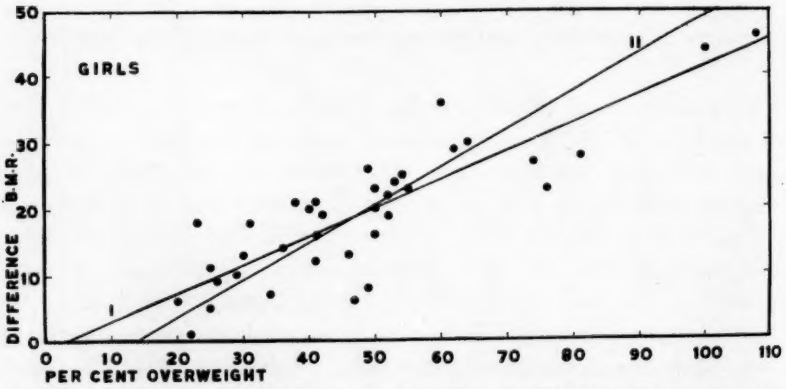


Chart 3.—Relation between excess in weight of girls and difference in basal metabolic rates computed from Talbot's height and weight standards. Line I indicates the prediction equation for difference in basal metabolic rates from weight excess. Line II represents the prediction of weight excess from the difference in basal metabolic rates.

and 0.865 for girls. The prediction of differences (Δ) in basal metabolic rates from weight excess (W) can be made from the equations:

$$\Delta = 0.44\ W + 1.3, \text{ for boys (line I in chart 2) and}$$
$$\Delta = 0.43\ W - 1.3, \text{ for girls (line I in chart 3).}$$

The prediction of percentage of weight excess from the difference between the two metabolic rates can be made from these equations:

$$W = 1.83\ \Delta + 7, \text{ for boys (line II in chart 2) and}$$
$$W = 1.74\ \Delta + 14, \text{ for girls (line II in chart 3).}$$

These equations represent straight lines, which are plotted in charts 2 and 3. The distribution of the individual cases is demonstrated in relation to the regression lines.

Since Talbot's height standards were obtained from the same figures as his weight standards, these lines should pass through the zero point if the figures from which they were calculated had been obtained under conditions identical with those under which the standards were deter-

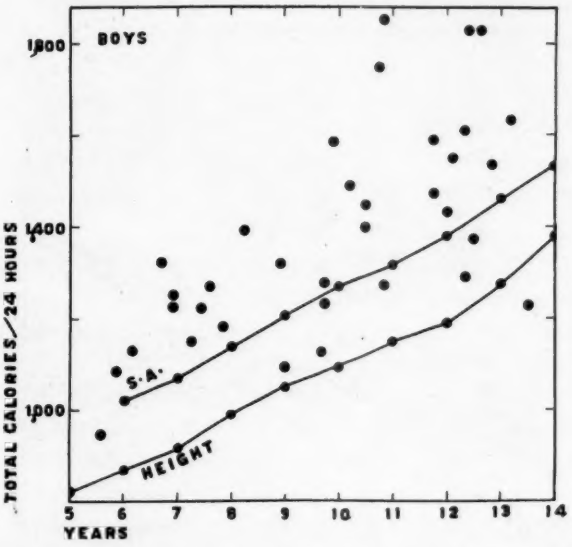


Chart 4.—Basal metabolism of obese boys expressed as calories per twenty-four hours compared with basal metabolism of normal children of the same chronologic age. *S. A.* designates the curve for normal children calculated from surface area standards; *height*, the curve for normal children calculated from Talbot's height standards. Chronologic age is expressed in years.

mined. The deviations in my equations find an explanation in differences in the technic of determination of basal metabolism and in variations in the calculation of the excess of weight.

The values for surface area and height-weight standards give marked differences in the computation of the basal metabolic rates for normal children; no attempt was made to calculate a correlation between the difference of these values and the excess of weight.

The total metabolism in these cases, expressed as calories per twenty-four hours, has been compared to the predictions for normal children of the same age (charts 4 and 5). The curves for height have been con-

structed from the figures for height in Burgess'[24] charts, in which the fiftieth percentile represents the mean height for a given age, and from Talbot's prediction of basal metabolism for standing height. The weight curve would fall somewhat above the height curve; they did not coincide, as might be expected since different height and weight standards from the one used by Talbot were used in the computations. The curves for surface area have been prepared by using the same values for standing height and for weight for height and age, those in the Baldwin-Wood[18]

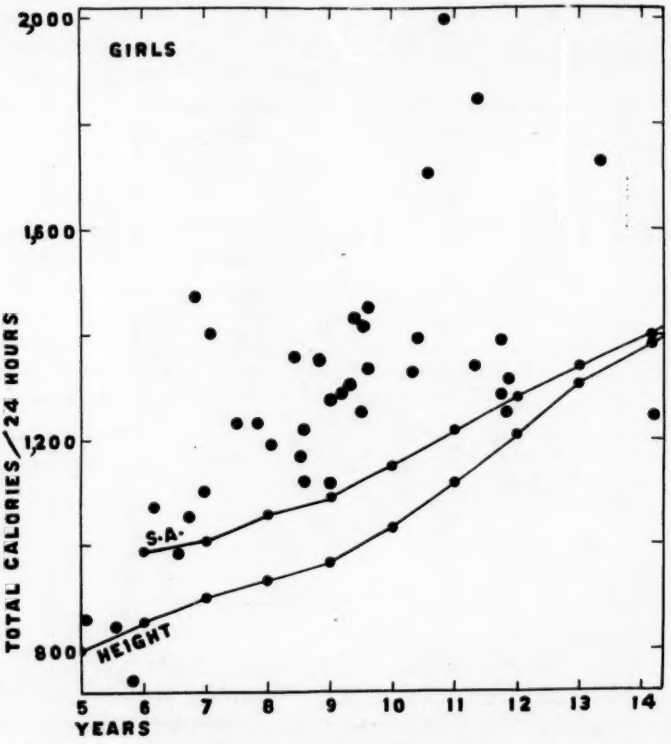


Chart 5.—Basal metabolism of obese girls expressed as calories per twenty-four hours compared with basal metabolism of normal children of the same chronologic age. *S. A.* designates the curve for normal children calculated from surface area standards; *height,* the curve for normal children calculated from Talbot's height standards. Chronologic age is expressed in years.

tables. From these figures, the surface area and the corresponding caloric requirement were computed according to the tables of Boothby and Sandiford. The difference between the normal prediction from surface area standards and from height-weight figures approached 10 per

24. Burgess, M. A.: The Construction of Two Height Charts, J. Am. Statist. A. **32**:290, 1937.

cent. By comparing the standards reported by different authors, Lewis and his co-workers [4] observed a similar deviation between the two standards. With the exception of 1 of the older boys and 1 girl, all obese children had values more or less above the curves which indicate the basal requirements for normal children of the same age. This presentation exaggerates the prevailing condition, since obese children are taller for their age than nonobese children. The same finding of a higher total metabolism is also demonstrable in the majority of observations if one chooses to plot the results according to height age instead of chronologic age; this relation has found its expression already in the high basal metabolic rates calculated from the height standards. The comparison to chronologic age appears justified since chronologic age is the only numerical description which is comparable with that of normal children. All other measuring units represent unequal stages of development.

An attempt was made to use the correction proposed by de Bruin.[6] The values for excessively heavy children—those 75 per cent and more overweight—did not conform better to the standard curve with than without the correction.

CHOLESTEROL

Determinations of serum cholesterol were done for 43 boys and 46 girls. Except in 1 case (case 9, table 1), no endocrine treatment had been used during the few months preceding the examination, as far as could be elicited from the history. In a number of cases more or less effective dietary restriction had been attempted; it was impossible to evaluate the magnitude and duration of this factor. On the whole, the recorded initial values can be considered as characteristic for untreated obesity.

The level of serum cholesterol scattered widely, varying from 108 mg. to 301.3 mg. per hundred cubic centimeters (tables 1 and 2). The mean value showed little difference between the sexes; it was 205.3 for boys and 195 for girls. The mean for the whole group of 89 children was 200.3 mg. per hundred cubic centimeters, with a standard deviation of $\pm$ 37.9.

The ratio of combined to free cholesterol ranged from 2.12 to 3.36. The average for the whole group was 2.6, with a standard deviation of $\pm$ 0.24.

The distribution of the total cholesterol for the different ages is presented in chart 6, which does not reveal a trend in the distribution of the figures with progressing age. The number of data for the different age groups is too small to be dealt with statistically. In addition, obese children show such varying degrees of maturity that the chronologic age says little about the degree of biologic development.

In chart 7 the values for total cholesterol are charted according to the degree of obesity. No relation could be established between the degree of obesity and the level of serum cholesterol. High values are

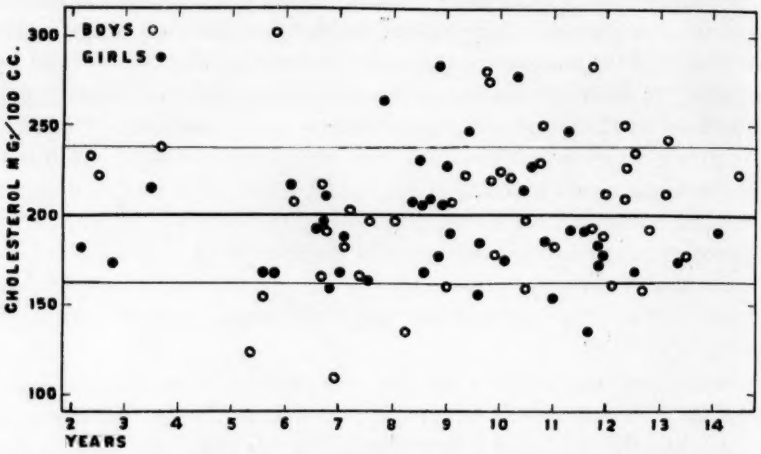


Chart 6.—Initial values for serum cholesterol, arranged according to chronologic age. Cholesterol values are given as milligrams per hundred cubic centimeters of serum. Chronologic age is expressed in years. The three horizontal lines indicate the mean of the cholesterol values and the standard deviation.

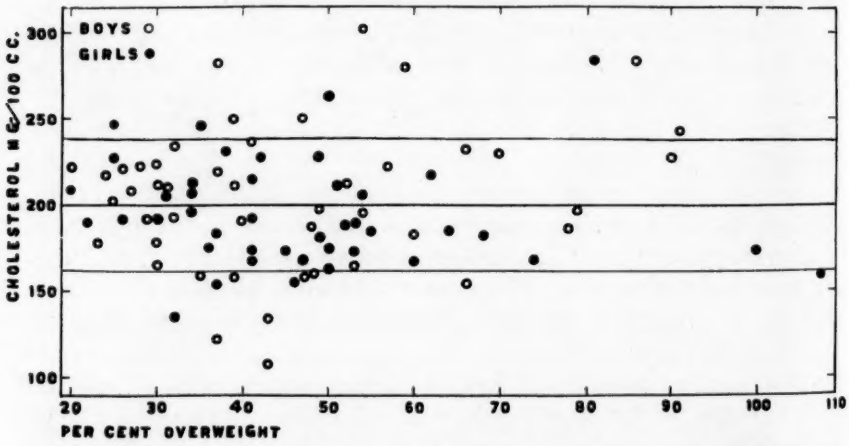


Chart 7.—Initial values for serum cholesterol, arranged according to weight excess expressed as percentage. The three horizontal lines indicate the mean of the cholesterol values and the standard deviation.

observed for moderately fat children and low figures for excessively fat children, and vice versa.

Further attempts to correlate the cholesterol level with other clinical findings, such as distribution of fat tissue, height development, bone

age, sexual maturation, race and duration of obesity were equally unsuccessful.

The relation of the cholesterol level to the basal metabolic rate for surface area and for standing height are illustrated in chart 8. It was hoped that a grouping of the cholesterol values might indicate which of the widely divergent basal metabolic rates represented the more correct picture of the metabolism. No relation could be detected between the cholesterol level and either of the basal metabolic rates.

It had been planned to study the influence of administration of thyroid and its withdrawal on the behavior of the cholesterol level in the course of treatment. In untreated congenital hypothyroidism a cholesterol level within the normal range is not infrequently observed. If

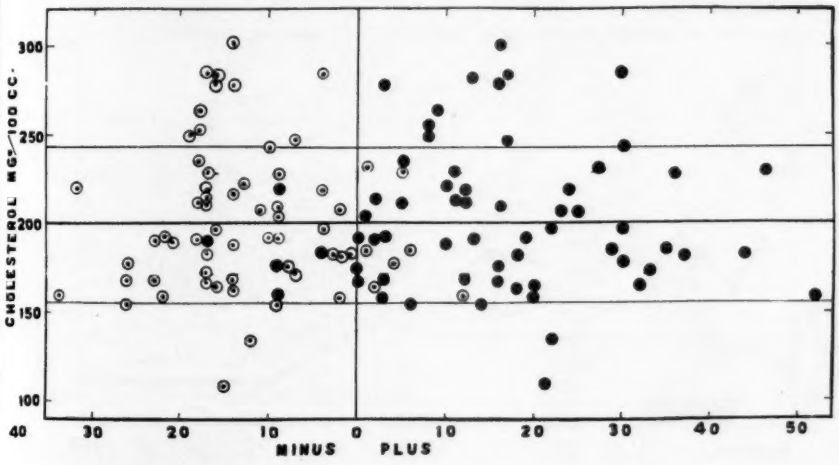


Chart 8.—Initial serum cholesterol concentration compared with basal metabolic rates calculated from two different standards. The solid dots represent the values computed by height standards; the circles with the central dot, the values computed by surface area standards. The three horizontal lines indicate the mean of the cholesterol values and their standard deviation; the vertical line, the "normal" basal metabolic rate.

thyroid is given for some time and then withheld, the previously normal cholesterol level rises. If hypothyroidism plays a significant role in obesity, one might expect a similar behavior of the cholesterol level. My observations, however, were complicated by the circumstance that dietary restriction was instituted simultaneously. In a number of cases a significant drop in serum cholesterol was observed after the food intake was reduced. This observation needs further elaboration and continues to

be an object of investigation. No statistical evaluation of this finding will be attempted in this paper.

I wish to illustrate the effect of administration of thyroid—or rather the absence of effect—in 2 cases. The course of the total cholesterol level during the treatment of patient G. T., a boy of 11 years and 9 months at the beginning of the period of observation (case 34, table 1), is illustrated in chart 9. Photographs of this patient were published previously.[25] The cholesterol level was 284 mg. per hundred cubic centimeters at the beginning of treatment. Restriction of diet and the resulting loss in weight were associated with a marked drop in the cholesterol level. Administration of 3 grains (0.19 Gm.) of thyroid[26] a day for six weeks did not lead to a faster drop; on the contrary, a

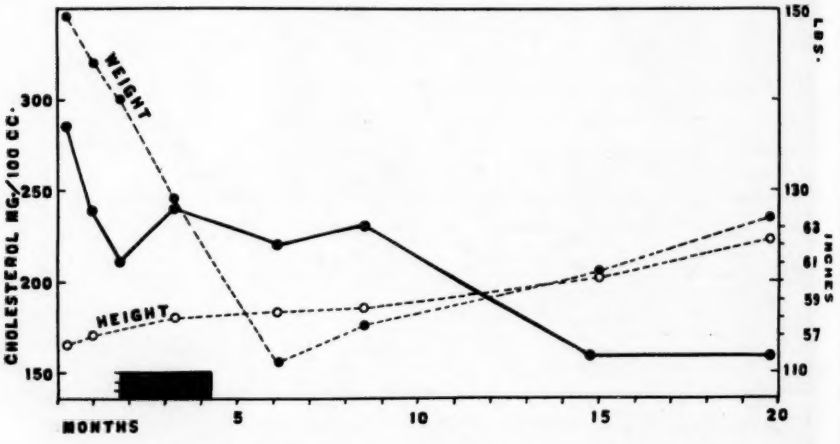


Chart 9.—Changes in the serum cholesterol concentration in the course of treatment of patient G. T. (case 34, table 1). Cholesterol values (heavy black line) are given as milligrams per hundred cubic centimeters of serum. Height and weight are expressed in pounds and inches. Thyroid medication is indicated by the solid black area at the bottom in 1 grain (0.06 Gm.) units per day. Time is expressed in months.

fluctuation toward a higher value was noticed. Its withdrawal was not followed by a rise of the blood cholesterol, nor was the rate of loss of weight influenced by its administration. It is interesting to note that this patient's level of serum cholesterol was maintained on a new "constitutional" level after his weight-height relation was stabilized. No significant changes in the ratio of free to combined cholesterol were noted

25. Bruch,[17] figure 12.

26. Burroughs, Wellcome thyroid, a 3 grain (0.19 Gm.) dose of which is equivalent to 9/10 grain (0.06 Gm.) of U. S. P. thyroid.

throughout the period of observation. The boy passed into puberty during this time. There was no indication from the observations that the pubertal changes affected his cholesterol metabolism.

The course of the total serum cholesterol concentration in a girl of 6 years and 10 months at the commencement of the period of observation (case 11, table 2) is presented in chart 10. This patient showed no signs of pubertal change while being studied. Although her serum cholesterol level was only 159 mg. per hundred cubic centimeters when treatment was started, the curve shows a course similar to that of the boy just described. There was a marked drop in the total cholesterol concentration after the food intake was reduced. Both children were strikingly obese and had been eating large quantities of food, mainly carbohydrates. Thyroid medication did not influence the rate of loss of

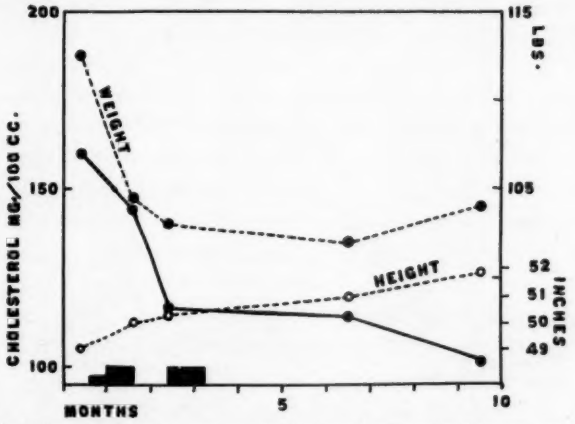


Chart 10.—Changes in the serum cholesterol concentration (heavy black line) in the course of treatment of patient G. B. (case 11, table 2). The construction of this chart is similar to that of chart 9.

weight or the drop in the cholesterol level. Similar observations, which failed to show an influence of thyroid medication on the cholesterol level and body weight, were made in a number of other cases.

One might raise the objection that the thyroid was given for too short a period to have a modifying influence on the cholesterol metabolism. One patient in our series (case 9, table 1), a boy of 6 years and 8 months, had received thyroid for several years in treatment of his obesity. No significant change in the cholesterol concentration was noticed during ten weeks of observation during which thyroid medication was interrupted (chart 11). The dietary regimen was not altered during that period. For comparison the changes in the serum cholesterol content of 3 hypothyroid patients of comparable age are presented. These patients, 1 boy, R. E., 7 years and 6 months old, and 2 girls, E. S., 5 years and 4 months, and J. A., 6 years and 9 months old, suffered from

congenital hypothyroidism and had received thyroid for several years, with excellent results. In fact, in regard to one of them, E. S., considerable skepticism had for a time been felt concerning the existence of hypothyroidism and its degree of severity. In all 3 cases, the interruption of thyroid medication was followed by a significant rise of the total cholesterol. There was a slight increase in weight but no progressing accumulation of fat tissue.

COMMENT

The wide disparity of results obtained by different computations of the basal metabolic rate confronts me with the difficult task of explaining the differences and, if possible, interpreting their clinical significance.

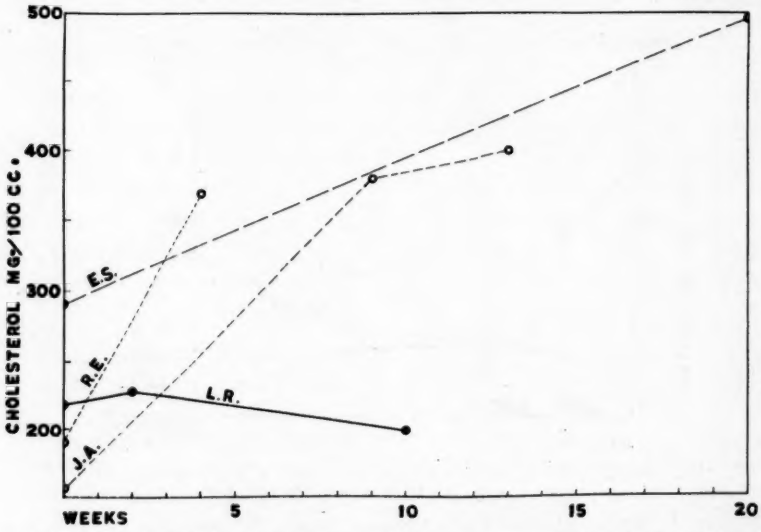


Chart 11.—Changes in the serum cholesterol concentration in 1 obese patient, L. R. (case 9, table 1) (solid line) and in 3 patients suffering from congenital hypothyroidism (broken lines) after the interruption of long-continued thyroid medication. All 4 curves start on the day when thyroid treatment was discontinued. Time is indicated in weeks. The cholesterol values are given as milligrams per hundred cubic centimeters of serum.

Since the populations used in computing standards of reference for basal metabolism of children were not identical in the group in which surface area was used as a criterion [23] and in the group in which height and weight were related to heat output,[22] it is not surprising that rates calculated by the various standards fail to coincide, even when subjects of average body build are involved. This circumstance explains in part the lower rates obtained from surface area standards. In addition,

by the first-mentioned standard different values are used for various ages; the predicted calories per square meter per hour are higher for a young child than for an adolescent or an adult. For example, the value for a girl of 9 years is 11.6 per cent higher than that for a 13 year old girl. Now, maturation, since it affects bodily configuration, has an influence on the relation of surface area to the mass of metabolically active tissue. It may also affect the output of energy in other less obvious ways. It is known that in obese children maturation frequently progresses faster than in normal children. As an instance of the difficulties encountered in this study, the case of an obese girl of 9 years whose surface area was as great as that of an adult woman and whose biologic maturation corresponded to that of an average girl of 13 years may be considered. By what standards shall such a patient be judged? Shall a correction be applied in order to reconcile the discrepancies among the functions involved—chronologic age, total mass and body configuration—and, if so, how shall one compute it? In the light of present knowledge it does not appear possible in each individual case to evaluate accurately the degree of deviation from normal development; and when the subjects under investigation are children of different degrees of deviation from an average pattern, deliberately selected, as in the present study, because of their excessive body weight, the validity of a comparison with any given norm on the basis of surface area may well be called into question.

It was possible to express the difference between basal metabolic rates from height and weight standards as a function of the excess in weight. But this throws no light on the fundamental underlying question as to which of the two rates represents the truer picture of the metabolic processes of an obese patient. It does not appear reasonable to try to use the results of calculations which are directly dependent on the degree of obesity as an explanation of the occurrence or severity of the obesity.

Further investigation may eventually provide a better way of evaluating the result of a determination of basal metabolism. At the present all that is known is that the oxygen consumption of an obese child is higher than that of a normal child of the same age and height.

Studies of the basal metabolism of patients in different states of nutrition are generally based on the premise that the body is composed of two main types of tissue, one of which produces heat while the other does not. The active tissues include the muscles and organs; the fatty tissue is generally referred to as metabolically inactive.

Attempts have been made to evaluate the amount of muscle tissue from the urinary excretion of creatinine. Kahn and Smith [27] concluded

27. Kahn, P., and Smith, N.: The Rôle of Muscle in Obesity, Arch. Dis. Childhood **11**:31, 1936.

from their determinations that in the so-called obese child the increase in weight is as a rule due as much to an increase of muscle as to an increase of fat tissue. Talbot,[28] defining obesity strictly as an accumulation of subcutaneous fat, found changes in weight for height neither qualitatively nor quantitatively accurate as an index of obesity. Comparison of the results of determinations of basal metabolism with the creatinine coefficient promises to give results as satisfactory as or better than those based on the relation to height or to weight.

An attempt was made to evaluate the relation of weight excess to differences between nasal metabolic rates from this point of view. Clinical estimation of the relative amount of muscle and fat tissue in children in whom the difference was smaller than was expected (marks that fall below the regression lines in charts 2 and 3) suggested that in these children the muscles are comparatively well developed. This conclusion needs confirmation through assessment of the amount of muscle by the study of the urinary creatinine or by some other method.

Though further investigation in this direction will help to clarify part of the problem of relating the basal metabolism of an obese child to some standard unit, it will not answer the whole question. The old premise that fat tissue is metabolically inert is in need of revision. Recent investigations of the intermediary metabolism of fatty acids by Schoenheimer [29] led to the conclusion that "contrary to the general idea of the slow metabolism of fat tissues, all the experiments above outlined point to the fact that the fat stores are very actively involved in the conversion processes characteristic of life." Nothing is known as to the extent to which this is true for the enormous fat deposits of obese persons. It may or may not be that the fat tissues of obese persons are physiologically different from those of normal persons or that there are different types of obesity, in which the behavior is different. Until more is known about the metabolism of normal and of pathologic fat tissue, the subcutaneous fat tissue, in whatever way its amount is assessed, cannot be discarded as metabolically inert. It appears likely that it acts as heat-producing tissue, though in a lesser degree than muscle. Benedict and Lee's [30] observations of the basal metabolism of different races

---

28. *(a)* Talbot, N. B.: Measurement of Obesity by the Creatinine Coefficient, Am. J. Dis. Child. **55**:42 (Jan.) 1938. *(b)* Talbot, N. B.; Stewart, A. H., and Broughton, F.: Basal Energy Metabolism and Creatinine in the Urine: II. Prediction of Basal Heat Production from Creatinine, Am. J. Dis. Child. **56**:965 (Nov.) 1938.

29. Schoenheimer, R.: The Investigation of Intermediary Metabolism with the Aid of Heavy Hydrogen, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 122.

30. Benedict, F. G., and Lee, R. C.: *(a)* La production de chaleur de la souris. Etude de plusieurs races de souris, Ann. de physiol. **12**:983, 1936. *(b)* Die Bedeutung des Körperfettes für die Wärmebildung im Organismus, Biochem. Ztschr. **293**:405, 1937.

of mice and of geese before and after fattening support the assumption that fat tissue increases the heat production of the body.

Another factor which tends to raise the metabolism is the increased rate of growth and maturation of obese children. As was pointed out previously in discussion of the surface area standards, neglect of this factor represents a source of error. There are other factors, such as overfeeding, emotional tension and labored breathing, which may add unknown quantities to the total sum of what is measured in determining the basal metabolism. These considerations are all in keeping with the observation made by many students of metabolism that the total metabolism of obese persons is increased. At present there is no way of measuring the amount of this increase, nor is there a basis for conclusions as to the clinical and pathogenetic significance of the determination of the basal metabolism of an obese child.

In this paper an attempt has been made to use the serum cholesterol values as additional evidence in evaluating the basal metabolism, with special reference to the problem of hypothyroidism. No relation between basal metabolic rate and cholesterol level was revealed. This finding makes it unlikely that hypothyroidism is of importance, if active at all, in the pathogenesis of obesity.

The normal range of the serum cholesterol values suggests the same conclusion. The average value in the group studied, 200.3 mg. per hundred cubic centimeters, is in good agreement with the figures reported by Sperry [31] for normal adults (209.8 mg. per hundred cubic centimeters) and by Offenkrantz and Karshan [32] for normal children (183.4 ± 46.8 mg. per hundred cubic centimeters). The values for the ratio of combined to free cholesterol were similar in all three groups. The failure of the serum cholesterol of obese children to react with a distinct rise to interruption of thyroid therapy is further evidence against an involvement of the thyroid gland.

Briskas' [16] observation of a high value for cholesterol in 22 of his 117 patients may be explained by the circumstance that he included in his series patients who exhibited the obvious picture of childhood myxedema, whereas this study was limited to children in whom obesity was the outstanding feature.

CONCLUSION

The aim of this study has been to evaluate the usefulness of determinations of basal metabolism in the understanding of obesity. The figures observed and the correlations calculated lead to the conclusion

31. Sperry, W. M.: The Relationship Between Total and Free Cholesterol in Human Blood Serum, J. Biol. Chem. **114**:125, 1936.

32. Offenkrantz, F. M., and Karshan, M.: Serum Cholesterol Values for Children, Am. J. Dis. Child. **52**:784 (Oct.) 1936.

that determinations of basal metabolism as ordinarily carried out and as conventionally reported are an untrustworthy guide when the clinician is seeking to estimate the part played by the thyroid in the pathogenesis of obesity. The basal metabolism of obese children should remain the object of clinical research until the many unknown components which enter into its computation are better recognized and understood.

The same negative conclusion, that no clinically useful information can be obtained from it, must be drawn with regard to the value of single determinations of serum cholesterol. The lack of relation between the serum cholesterol concentration and the basal metabolic rate computed from different standards is strong evidence against the assumption that hypothyroidism plays an important role, if any, in the pathogenesis of simple obesity. The failure of thyroid medication and of its withdrawal to influence the cholesterol level is additional support for this conclusion. My previous observation of normal or accelerated growth and development of obese children pointed in the same direction.

These conclusions, however, do not imply that the intermediary metabolism and the endocrine balance of obese children are normal. Further investigation may eventually reveal some measurable dysfunction. At present, it is necessary to face the fact that the customary clinical and laboratory examinations do not furnish satisfactory clues as to the nature of the physiologic disturbance in obesity.

SUMMARY

Determinations of basal metabolism for 72 obese children and serum cholesterol determinations for 89 are reported.

The total basal metabolism of obese children is higher than that of normal children of comparable height and age.

Calculation of the basal metabolic rate according to different standards furnishes widely diverging results, none of which can be considered the correct one.

Differences in the basal metabolic rates computed from Talbot's height and weight standards are proportional to the percentage of excess in weight. The correlation coefficient and prediction equations for these two factors are presented.

The mean value for the total serum cholesterol is 200.3 mg. per hundred cubic centimeters of serum, with a standard deviation of $\pm$ 37.9. The ratio of combined to free cholesterol is 2.60 $\pm$ 0.24.

No relation between the serum cholesterol concentration and the basal metabolic rate is revealed in this study.

Thyroid medication and its interruption fails to influence the serum cholesterol concentration and the rate of loss of weight.

AIR CONTAMINATION AND AIR STERILIZATION

E. CHANT ROBERTSON, M.D., PH.D.

M. ELIZABETH DOYLE, B.H.Sc., M.A.

FREDERICK F. TISDALL, M.D., F.R.C.P. (CANADA)
TORONTO, CANADA

LEWIS R. KOLLER, PH.D.
SCHENECTADY, N. Y.
AND
FRANCIS S. WARD, B.Sc.
TORONTO, CANADA

If secondary infections could be avoided in hospital wards, both the patients and the hospital would be greatly benefited. Until a few years ago, these infections were thought to be carried either by the attendants' hands or by droplets coughed out by the patients. Such droplets travel only a few feet, and sufficient space between the beds would control this mode of spread. However, the work of W. F. Wells and M. W. Wells [1] has shown that bacteria in very small particles, or "nuclei," can remain suspended in the air for two or three days, and this strongly suggests that air-borne bacteria may play a part in the spread of disease in the wards.

That ultraviolet lamps can be used to kill air-borne bacteria has been demonstrated by several investigators. For example, Hart [2] reported that when he operated under a battery of eight tubular ultraviolet lamps, the wounds in extensive operations showed infection less frequently and healed more rapidly and less postoperative pyrexia developed. When the lamps were used, few organisms grew on agar plates set out in the operating room. Without the lamps the counts were much higher.

Read at the Seventeenth Annual Meeting of the Canadian Society for the Study of Diseases of Children, Alexandria Bay, N. Y., June 16, 1939.

Dr. Robertson, M. Elizabeth Doyle and Dr. Tisdall are associated with the Department of Pediatrics, University of Toronto, and the Hospital for Sick Children; Dr. Koller, with the Research Laboratory of the General Electric Company, and Francis S. Ward, with the Air Conditioning Division of the Canadian General Electric Company, Ltd.

1. (*a*) Wells, W. F.: On Air-Borne Infection, Am. J. Hyg. **20**:611, 1934. (*b*) Wells, W. F., and Wells, M. W.: Air-Borne Infection, J. A. M. A. **107**: 1698 (Nov. 21) 1936; Air-Borne Infection: Sanitary Control, ibid. **107**:1805 (Nov. 28) 1936.

2. Hart, D.: Sterilization of the Air in the Operating Room by Special Bactericidal Radiant Energy, J. Thoracic Surg. **6**:45, 1936.

Ventilating the room with washed air also reduced the number of air-borne bacteria. A similar type of air-sterilizing unit was tested by Robertson and Doyle [3] in one of the operating rooms of the Hospital for Sick Children, Toronto, Canada. An air-changing system was also present in this room. The bacteria in the air were counted by means of an air-sampling device. Both the air changing and the ultraviolet radiation, especially the latter, reduced the number of air-borne bacteria, and the combination of the two was the most effective. McKhann and his associates [4] and Wells [5] found an ultraviolet ray barrier in a corridor effective in preventing the spread of chickenpox in an isolation ward. Wells [6] reported an experimental study in which ultraviolet ray barriers prevented bacteria from passing from one part of a room to another. The effect of air changing was not included in this study, although Wells and Wells [1b] and Whisler [7] had previously shown that strong sources of ultraviolet rays killed large numbers of bacteria even in rapidly moving air.

To gain information regarding the most effective way of preventing air-borne bacteria coughed by one patient from reaching another, one of the rooms in the laboratory was converted into a small model ward. The room was about 21 feet by 12 feet (640 by 366 cm.), with a ceiling 9 feet (274 cm.) high. It was divided into four cubicles or stalls, each about 5 feet by 4 feet (152 by 122 cm.), by partitions that ran from the floor to the ceiling, as shown in the floor plan (fig. 1). The upper 2 feet 10 inches (86 cm.) of the front opening into each cubicle was closed by a partition extending down from the ceiling. If this were an actual ward, the babies' cots would be placed near the back of these cubicles.

The air-changing system for this room was designed by one of us (F. S. W.). The ducts were made of heavy cardboard, so that alterations could be made easily. The air in the room could be circulated at the rate of one to twelve times an hour. Any proportion of fresh air from 10 to 90 per cent could be introduced, the rest of course being recirculated, or used, air. The air entered the cubicles near the floor at the back (*S*, fig. 2) and was removed near the ceiling (*R*, fig. 2). The ceiling outlets were used because in an actual ward the air coughed out

3. Robertson, E. C., and Doyle, M. E.: On the Control of Air-Borne Bacteria in Hospitals, Ann. Surg., to be published.

4. McKhann, C. F.; Steeger, A., and Long, A. F.: Hospital Infections: Survey of the Problem, Am. J. Dis. Child. **55**:579 (March) 1938.

5. Wells, W. F.: Air-Borne Infections, Mod. Hosp. **51**:66, 1938.

6. Wells, W. F.: Measurement of Sanitary Ventilation: II. Infection of Air, read before the American Public Health Association, Oct. 27, 1938.

7. Whisler, B.: The Effect of Ultraviolet Radiation upon Bacteria Suspended in the Air, unpublished thesis, Harvard University, May 1936.

or exhaled by the child would tend to rise. However, at the low rates of air flow used in these tests, it was found that local air currents and eddies were sufficient to cause some of the air discharged in one cubicle to travel around into an adjacent cubicle before going to an outlet.

In our experience it was not feasible to have doors across the front of the cubicles, so a curtain of ultraviolet rays was used instead. General Electric germicidal lamps were used. These are low pressure

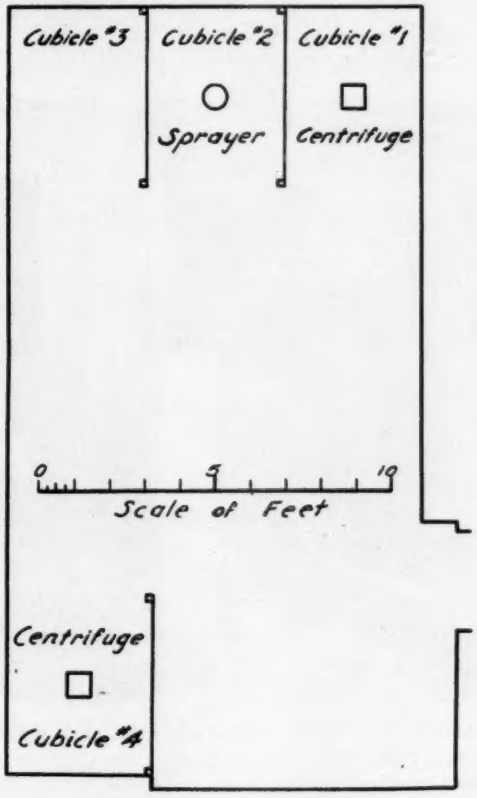


Fig. 1.—Floor plan of experimental room.

mercury vapor lamps in glass which transmits ultraviolet rays. They are tubular, measure 18 inches in length and 1 inch in diameter (46 by 2.5 cm.) and operate at 60 volts. Ninety-five per cent of the radiation emitted is at the wavelength of 2,537 angstroms. This is considerably shorter than the shortest ultraviolet ray in summer sunshine. The amount of ozone produced by these lamps is so small that it would not be harmful. Two lamps were placed above, shining down (*L*, fig. 2), and two were mounted vertically on each side so as to throw a curtain

across from the sides (L_1, fig. 2). The vertical lamps were placed below the eye level of adults (below 4 feet, or 122 cm.). The lamps were baffled to protect the eyes and skin of the patients and staff from the ultraviolet rays. The baffles we used were made of cardboard, but any nonreflecting material would serve. They were set parallel and as close as possible to the lamps and extended out about 4 inches (10 cm.) on each side of the lamps (fig. 3). The lamps across the top and on the walls of the room would have been more efficient if some type of parabolic reflector had been used in conjunction with the nonreflecting baffles. One of us (L. R. K.) measured the distribution of ultraviolet

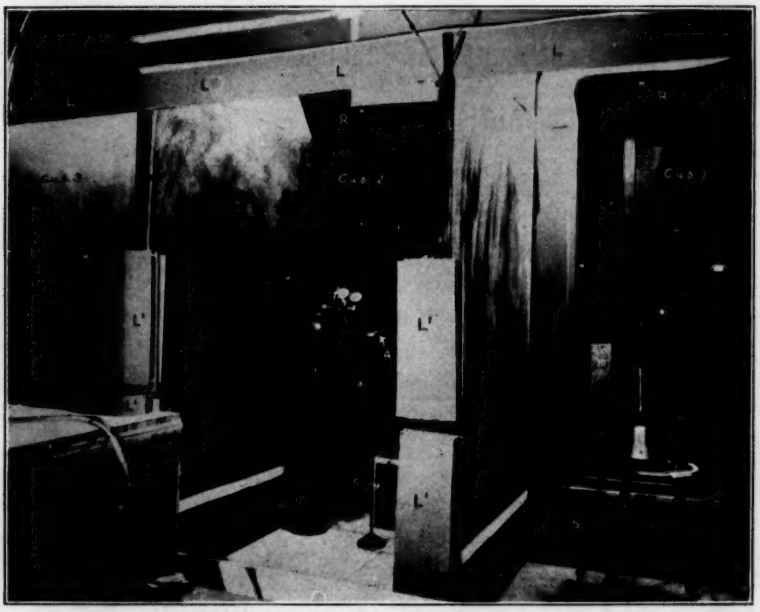


Fig. 2.—The experimental room, looking into cubicles 1, 2 and 3. A Wells air centrifuge is shown in cubicle 1. *S*, air supply; *R*, return; *A*, atomizer for spraying bacteria; *L*, baffles shielding top ultraviolet lamps; L^1, baffles shielding side ultraviolet lamps; *W*, partition wall extending from lamps to cieling.

radiation with a photo-electric cell set 2 feet (61 cm.) away from the lamps. Most of the ultraviolet radiation was in a beam 6 inches (15 cm.) wide at this distance. With the method used, no radiation could be detected back in the cubicle where the baby would be placed. Although a more sensitive detector would no doubt reveal the presence of ultraviolet radiation in these areas, we can safely conclude that it was negligible.

Usually broth cultures of Bacillus prodigiosus were sprayed from a fine glass atomizer (*A*, fig. 2) with a 10 pound pressure of compressed

air in cubicle 2 (fig. 1). Occasionally cultures of Bacillus coli or Sarcina were used instead. Samples of air were then collected at intervals with Wells air centrifuges [8] simultaneously in the adjoining cubicle (cubicle 1) and across the room (cubicle 4). The Wells centrifuge is an instrument for counting the bacteria in a known quantity of air. The atomizer was of the type formerly used for spraying 1 : 100 solutions of epinephrine into the trachea, and it produces a very fine spray. The atomizer and the intakes of the Wells centrifuges were approximately 3½ feet (107 cm.) above the floor (about the height of a baby's cot). The agar was run up in the Wells centrifuge tubes before use, so that one minute samples, drawing in known amounts of air, could be taken during the experiment. The amounts of air in the different tests varied from 1.5 to 2 cubic feet, and the number of bacteria per cubic foot was determined (tables 1

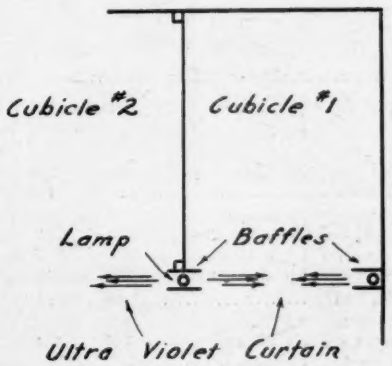


Fig. 3.—Section through cubicles 1 and 2 to show the arrangement of the baffles.

to 9). Usually the culture was sprayed for two minutes and air samples were taken immediately and after gradually increasing intervals.

GENERAL PLAN OF EXPERIMENTS

We planned to test the efficiency of the following means of removing the bacteria from the air: (1) air changing only, (2) ultraviolet ray curtains across the entrances to the cubicles, (3) ultraviolet lamps in the ducts (in this case the samples were taken from the ducts before and after the air passed the lamps) and (4) ultraviolet ray curtains across the entrances to the cubicles and ultraviolet lamps in the ducts, with and without air changing.

1. *Air Changing Only.*—When the air-changing system was not used the bacteria produced by two minutes' spraying disappeared from the

8. Wells, W. F.; Phelps, E. B., and Winslow, C.-E. A.: A Bacteriological Method of Sanitary Air Analysis, Am. J. Pub. Health (supp.) **27**:97, 1937.

air, as shown in experiment 1 of table 1. The rapid decrease in the number of bacteria is due to several causes, such as their dropping to the floor, dilution with the air of the rest of the room and dilution by natural infiltration of outside air. The air-changing system was then turned on at the rate of four air changes per hour, 50 per cent of the

TABLE 1.—*Effect of Air Changing Only*

		Bacteria per Cubic Foot of Air; Samples Taken in Cubicle 1						Minutes of Spraying
	Time after spraying was started, minutes.....	2	4	8	16	32	64	
Experiment 1	No air changing.....	2,762	713	87	8	3	0	2
Experiment 2	Four air changes per hour (50 per cent fresh air)...	1,128	241	46	6	0.5	0	2

TABLE 2.—*Effect of Ultraviolet Ray Curtain with No Air Changing* *

			Bacteria per Cubic Foot of Air; Samples Taken in Cubicle 1					
Number of Lamps	Time after spraying was started, minutes		2	4	8	16	32	64
(*a*) Two top lamps only	Experiment 1	No lamps No air changing	570	194	26	8	0	0
	Experiment 2	Ultraviolet lamps No air changing	111	15	0.8	0	0	0
	% Killed	.....	80	92	99.7	100	..	..
(*b*) Two top lamps and one at sides, lower	Experiment 3	No lamps No air changing	384	166	8	0	0	0
	Experiment 4	Ultraviolet lamps No air changing	69	16	0	0	0	0
	% Killed	.....	82	90.5	100	..	..	..
(*c*) Two top lamps and one at sides, alternate upper and lower	Experiment 5	No lamps No air changing	234	178	45	5	1	..
	Experiment 6	Ultraviolet lamps No air changing	50	15	1.3	0	0	..
	% Killed	.....	79	92	97	100	100	..
(*d*) Two top lamps and two at sides	Experiment 7	No lamps No air changing	470	315	100	22	11	2
	Experiment 8	Ultraviolet lamps No air changing	0.6	0.5	0	0	0	0
	% Killed	.....	99.9	99.9	100	100	100	100

* Two minute sprayings were used in all these experiments.

air being fresh. The same culture of bacteria was again sprayed for two minutes, and the results shown in experiment 2 of table 1 were obtained. The air changing reduced the number of bacteria in the air. This of course was not surprising, as about 6,400 cubic feet of bacteria-laden air was being forced out of the room in an hour. These results were confirmed in four other experiments.

2. *Ultraviolet Ray Curtain Only.*—Similar tests were carried out in which (1) bacteria were sprayed and collected while neither the air-changing system nor the ultraviolet lamps were operating and (2) the same culture was sprayed immediately afterward but with the ultraviolet lamps on and samples were collected.

The intensity of the ultraviolet curtain could be varied according to the number of lamps used. We tested the effects of (*a*) the two top lamps mounted above each cubicle entrance and shining down (fig. 4 *A*), (*b*) the two top lamps and only the lower one of the two side lamps (fig. 4 *B*) and (*c*) the two lamps and only one of the side lamps, the upper and lower ones being used alternately (fig. 4 *C*).

Within two minutes these arrangements of the lamps killed 79 to 82 per cent of the bacteria (table 2) when the number of organisms in

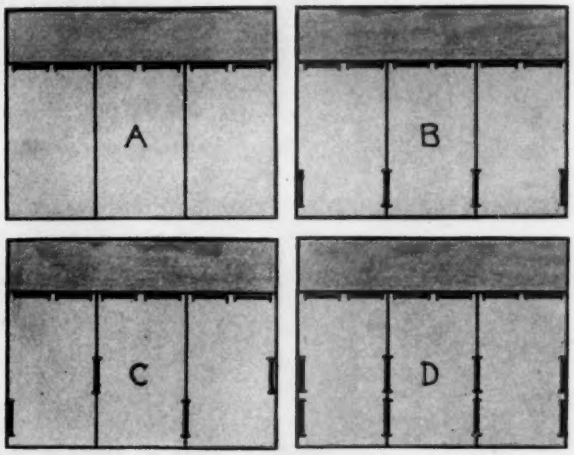


Fig. 4.—The entrances to cubicles 1, 2 and 3, showing the different arrangements of ultraviolet lamps: *A*, two top lamps only; *B*, two top lamps and one side lamp (lower only); *C*, two top lamps and one side lamp (upper and lower alternately), and *D*, two top lamps and two side lamps. The top lamps were about 6 feet 2 inches (188 cm.) from the floor.

the air was within the range found in the most contaminated parts of the hospital. (In previous tests we found the most bacteria in the crowded hall of the outpatients' department, where there were as many as 336 organisms of various kinds per cubic foot of air.) When the number of bacteria in the air was very high, i. e. over 1,000 per cubic foot, the percentage killed was higher. Numerous tests were carried out with these arrangements of the lamps. Those shown in table 2 are typical.

We felt that these arrangements were not the most effective possible, and we therefore tested the effect of (*d*) the two top lamps plus the two side lamps (fig. 4 *D*). With this arrangement over 95 per cent of the

bacteria were regularly killed, as is shown in experiments 7 and 8 of table 2, which are typical of many such experiments. Similar results were obtained when the counts were made in cubicle 4, although all the figures were lower. Figure 5 shows the Wells centrifuge tubes with the results obtained in one of these tests.

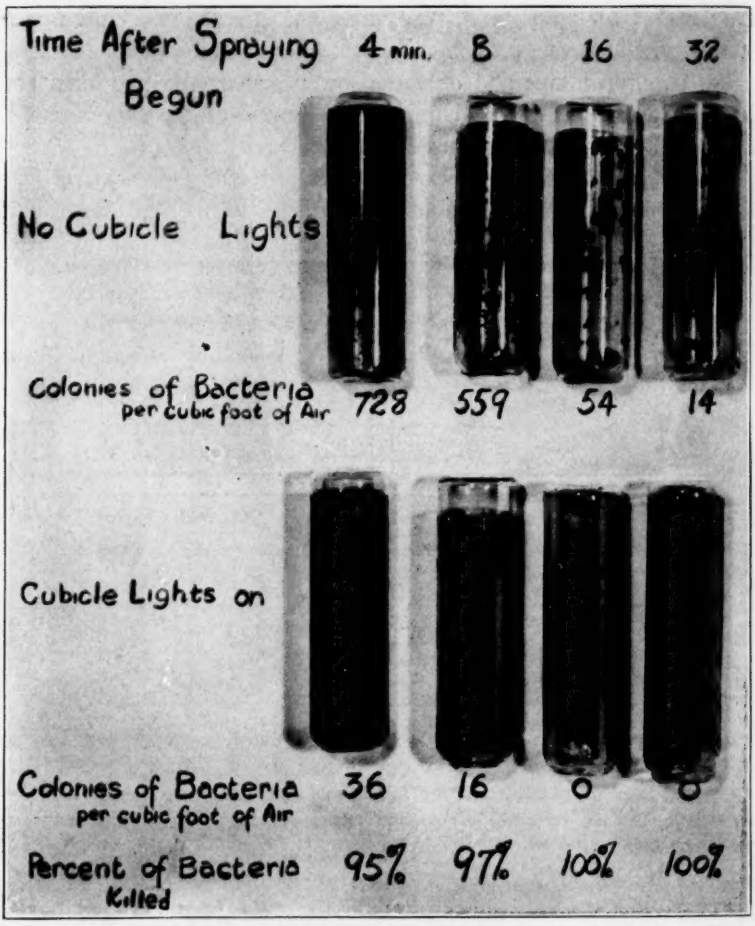


Fig. 5.—Bacterial growth in Wells centrifuge tubes showing the killing of airborne bacteria by ultraviolet lamps in cubicle 1. Bacteria were sprayed at a constant rate for eight minutes. The upper row shows the gradual decrease in bacteria due to settling out after the spraying was stopped. The lower row shows the rapid disappearance when ultraviolet light was used, even while the sprayer was still on.

In order to compare the number of bacteria in the cubicle where the sprayer was placed (cubicle 2) with that in the next cubicle (cubicle 1), the following tests were carried out: With all the ultraviolet lamps in

the cubicles on but with no air changing, air samples were taken simultaneously in the two cubicles. As can be seen in table 3, very few organisms were able to pass through the ultraviolet curtain out of cubicle 2 and through the ultraviolet curtain into cubicle 1.

B. coli was about as hard to kill with the ultraviolet rays as B. prodigiosus. When sarcinae, which are large air-borne cocci growing in packets of eight, were used, the rays were much less effective. For example, when cultures of B. prodigiosus and sarcinae were mixed in equal parts and sprayed, the results shown in table 4 were obtained.

TABLE 3.—*Effect of All Ultraviolet Lamps in Cubicle with No Air Changing*

	Bacteria per Cubic Foot of Air					Minutes of Spraying
Time after spraying was started, minutes.....	2	4	8	16	32	
Samples taken beside sprayer in cubicle 2.....	27,000	21,000	29,400	11,630	3	16
Simultaneous samples taken in next cubicle (1)	153	106	91	117	..	16

TABLE 4.—*Equal Amounts of Cultures of B. Prodigiosus and Sarcinae*

		Bacteria per Cubic Foot of Air; Samples Taken in Cubicle 1												
Time after spraying was started, minutes.....		2		4		8		16		32		64		Minutes of Spraying
		B. prodigiosus	Sarcinae	B. prodigiosus	Sarcinae	B. prodigiosus	Sarcinae	B. prodigiosus	Sarcinae	B. prodigiosus	Sarcinae	B. prodigiosus	Sarcinae	
Experiment 1	No lamps No air changing	176	42	89	55	13	51	1	31	0.6	13	1	12	2
Experiment 2	Ultraviolet lamps on No air changing	11	27	1	53	0	19	0	9	0	9	0	8	2
	Percentage killed	94	36	97	4	100	37	100	71	100	31	100	33	

The ultraviolet radiation killed 94 to 100 per cent of the B. bacilli and only 4 to 71 per cent of the sarcinae. Sarcinae are resistant to lethal agents. However, it is possible that when bacteria are present in clumps some of them may escape the bactericidal effect of the lamps. A number of reports regarding the sensitivity to ultraviolet rays of various pathogenic and nonpathogenic organisms have been published.[9] Many investigators have found the pathogens more easily killed by ultraviolet rays; others have found no difference. One investigator found Bacillus diphtheriae harder to kill than B. prodigiosus, although the other pathogens that he used were more easily destroyed. One could reasonably

9. Duggar, B. M.: Biological Effects of Radiation, New York, McGraw-Hill Book Company, 1936.

conclude therefore that with one possible exception the pathogens are at least as easily killed as B. prodigiosus.

3. *Sterilization of Air in Ducts with Ultraviolet Rays.*—To investigate the possibility of using recirculated air in hospital wards, four of the ultraviolet lamps were mounted end to end along the duct which carried the used, or recirculated, air back to the cubicles. The duct was approximately 12 inches by 12 inches (30 by 30 cm.) and was lined with mat-finished aluminum foil. One Wells air centrifuge was connected by a rubber tube to a hole in the duct a short distance ahead of the lamps. The second Wells machine, connected in the same way, collected the air just after it had passed the lamps. The bacteria (B. prodigiosus) were sprayed into cubicle 2 as before, but for ten or fifteen minutes. Samples were taken at intervals during the spraying and also afterward, so that the effect of the lamps on small numbers of bacteria could be tested.

TABLE 5.—*Bactericidal Effect of Ultraviolet Lamps in the Ducts*

Rate of Air Flow		Bacteria per Cubic Foot of Air			
200 linear feet per minute	Number of lamps used	3	2	1	1
	Before passing lamps	12,525	44,020	12,300	849
	After passing lamps	6	66	88	25
	Percentage killed	99.9	99.9	99.3	97.1
450 linear feet per minute	Number of lamps used	4	4	4	4
	Before passing lamps	26,130	11,800	225	138
	After passing lamps	42	39	7	5
	Percentage killed	99.8	99.7	96.9	96.4

In the first test (table 5) the polluted air passed the lamps at the rate of 200 linear feet (61 m.) a minute. This was sufficient to change the air in the room four times an hour. Ninety-seven to 99 per cent of the bacteria were killed by passing one lamp. Figure 6 shows the Wells centrifuge tubes with results obtained in such a test. Other tests gave similar results. The effective parts of the lamps were about 16 inches (41 cm.) long. When the rate of air flow was increased to 450 linear feet (138 m.) a minute, the four ultraviolet lamps killed from 96 to 99 per cent of the bacteria passing down the duct, as shown in table 5.

4. *Ultraviolet Ray Curtain and Ultraviolet Lamps in Ducts, With and Without Air Changing.*—In these tests we thought it wise to use four ultraviolet lamps in the ducts and all the lamps on the cubicle partitions (fig. 4 *D*). One experiment was performed with all the lamps on but with no air changing and a second with all the lamps on and with four changes of air an hour (50 per cent fresh air). The results shown in table 6 were obtained. Poor growth of the culture was responsible for the small counts. These tests showed that four air changes per hour

did not reduce the effectiveness of the ultraviolet lamps. Previous tests had shown that one change per hour did not reduce it either. When the air changing was increased to nine changes per hour (50 per cent fresh air), the lamps did not seem to be as effective, as shown in table 7.

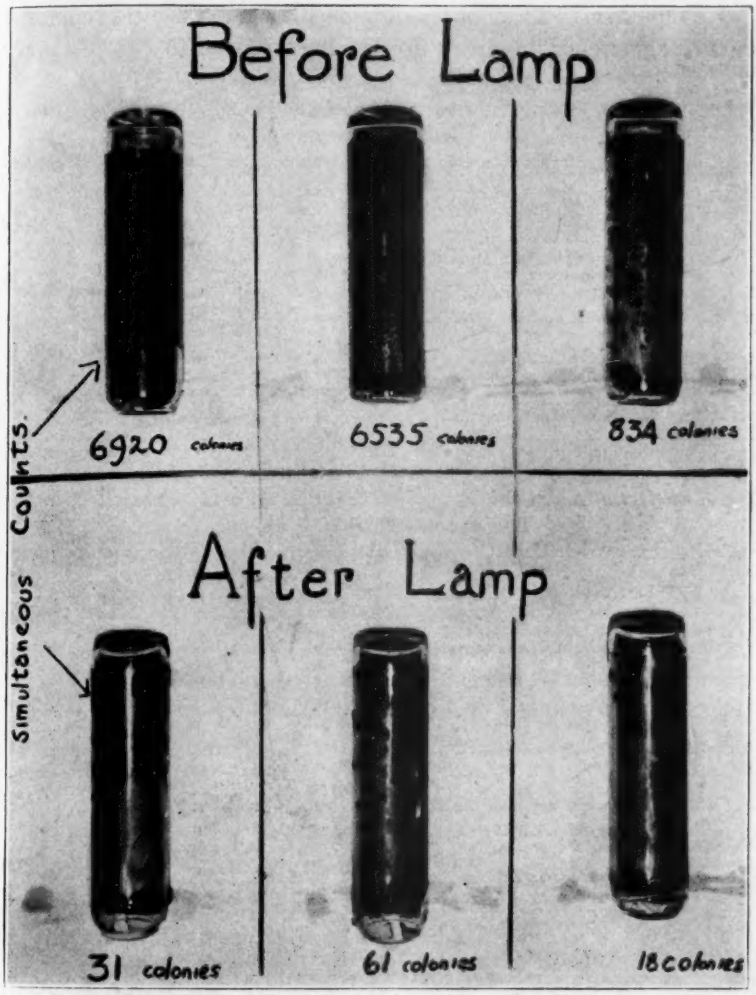


Fig. 6.—Bacterial growth in Wells centrifuge tubes showing the killing of airborne bacteria by one ultraviolet lamp in the air duct. The upper row shows that the air was heavily laden with bacteria before passing the ultraviolet lamp and the lower row that it contained few bacteria after passing the lamp.

It appears therefore that as long as the air motion is slow, the effectiveness of the lamps remains the same, but if the air motion is rapid, many organisms are able to pass through the barriers.

The Wells' Method.—Another method for testing the effectiveness of ultraviolet ray barriers has been devised by Wells, and we used it to check our earlier results. In this method, bacteria (B. prodigiosus) were sprayed continuously into cubicle 2 (fig. 1) until the number of bacteria in the air reached a constant figure. This figure was determined by taking samples every seven or ten minutes in the next cubicle (cubicle 1). Spraying for twenty-three to thirty minutes proved to be sufficient.

TABLE 6.—*Effect of Four Air Changes per Hour on the Effectiveness of Ultraviolet Lamps with All the Lamps on*

Experiment		Bacteria per Cubic Foot of Air; Samples Taken in Cubicle 1					Minutes of Spraying
	Time after spraying was started, minutes	2	4	8	16	32	
1	No air changing	14	11	21	0	0	8
2	Four air changes per hour	28	46	85	0	1	
3	No air changing	9	36	50	3	0	8
4	Four air changes per hour	8	14	26	0	0	
5	No air changing	9	36	50	3	0	8
6	Four air changes per hour	43	19	63	0	0	
7	No air changing	153	106	91	117	0	16
8	Four air changes per hour	44	75	99	37	..	

TABLE 7.—*Effect of Nine Air Changes per Hour on the Effectiveness of Ultraviolet Lamps with All the Lamps on*

Experiment		Bacteria per Cubic Foot of Air					Minutes of Spraying
	Time after spraying was started, minutes	2	4	8	16	32	
1	No air changing	9	36	50	3	0	8
2	Nine air changes per hour	116	62	22	0	0	
3	No air changing	13	21	0	0	0	4
4	Nine air changes per hour	36	32	0	0.5	0	
5	No air changing	67	103	201	0	0	8
6	Nine air changes per hour	196	332	87	0	0	
7	No air changing	128	..	..	..	..	8
8	Nine air changes per hour	342	..	..	..	..	
9	No air changing	153	106	91	117	0	16
10	Nine air changes per hour	18	13	21	60	2	
11	No air changing	67	103	201	0	0	8
12	Nine air changes per hour	3,763	4,750	5,390	14	0	

After this constant state had been reached, and with the sprayer still on, all the ultraviolet lamps on the cubicle walls were turned on and samples were taken every seven minutes in cubicle 1 (the adjacent cubicle) and in cubicle 4 (across the room). Ten cubic feet of air was collected in each sample. This took approximately five minutes per sample. Then, with the sprayer still on, the ultraviolet lamps were turned off and samples were again collected until a constant state was reached. Then the sprayer was turned off, and three samples were collected at seven minute intervals to show the die-away, or the rate at which the

bacteria dropped out of the air because of gravity, for instance, or dilution. In the first four of these tests air changing was not used.

The results of one of these tests are shown in table 8. The die-aways in this test were very slow, much slower than in the other three

TABLE 8.—*Wells' Method with No Air Changing*

	No. of Minutes After Sampling Was Begun	Bacteria per Cubic Foot of Air	
		Samples Taken in Cubicle 1	Samples Taken in Cubicle 4
No lamps	0	8,390*	12,570*
Lamps on (10 min.)	11	1,154	179
	18	94	6
	26	101	4
	33	60	3
	41	51	4
Lamps off (47 min.)	48	3,872	4,980
	55	7,165	8,177
	62	8,530	11,230
	69	8,005	13,2.0
	77	8,440	14,780
Sprayer off (83 min.)	84	8,060	19,750
	91	6,710	12,130
	98	5,395	14,250

* Equilibrium reached after twenty-three minutes.

TABLE 9.—*Wells' Method with Four Changes of Air per Hour*

	No. of Minutes After Sampling Was Begun	Bacteria per Cubic Foot of Air	
		Samples Taken in Cubicle 1	Samples Taken in Cubicle 4
No lamps	0	64*	106*
Lamps on (6 min.)	7	7	2
	15	0.7	1
	22	0.7	0.8
	29	2.0	0.5
	36	0.8	0
Lamps off (43 min.)	44	26	25
	51	24	30
	58	29	32
	64	18	36
	70	20	40
Sprayer off (76 min.)	77	20	14
	84	4	3
	92	1	0.6

* After thirty-five minutes' spraying.

tests. When the figures obtained in cubicle 1 are plotted, they give the curve shown in figure 7. By means of the formula utilized by Wells,[10] these figures can be used to determine the number of air changes per

10. Wells, W. F., and Wells, M. W.: Measurement of Sanitary Ventilation, Am. J. Pub. Health **28**:343, 1938.

hour that would be necessary to produce the same reduction in the number of air-borne bacteria as that produced by the lamps. When this formula is used on the counts obtained in cubicle 1, the lamps are shown to be equivalent to 158 air changes per hour. This is probably too low, because the die-away is slow. Mere inspection of the figures shows the lamps to be very effective.

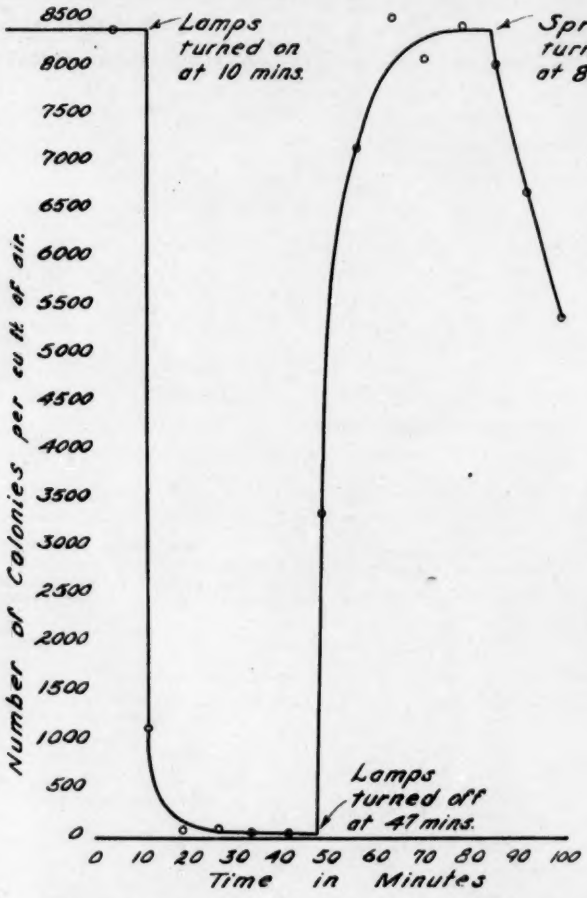


Fig. 7.—Destruction of air-borne bacteria by ultraviolet lamps. Bacteria were being sprayed into the air at a constant rate for the first eighty-three minutes of the test.

In a second test, in which the die-away was much faster, in cubicle 1 the effect of the lamps was equivalent to 662 air changes per hour. In the other two tests the formula could not be applied, as constant states were not attained. However, they all showed the marked bactericidal effect of the lamps.

A similar test was carried out when the air-changing system was on, providing four air changes an hour. The results are shown in table 9. The numbers of bacteria are low because, for some unexplained reason, the culture had grown poorly. It is doubtful whether the Wells formula should be applied to such small numbers. With it the effect of the lamps was shown to be equivalent in cubicle 1 to 141 changes per hour and in cubicle 4 to 510 changes per hour.

This study has shown that ultraviolet ray curtains can almost completely prevent the spread of air-borne bacteria from one part of a room to another. With this information to aid us, we are constructing a ward for infants in which we hope cross infections caused by air-borne bacteria will be much reduced. The results can be estimated only after prolonged clinical observations.

CONCLUSIONS

1. Barriers of ultraviolet rays produced by sterilizing lamps are effective in preventing the spread of artificially introduced bacteria (B. prodigiosus) from cubicle to cubicle in an experimental room.

2. Such lamps are very effective in killing bacteria in air ducts.

3. The lamps on the cubicle partitions are very effective when the air movement is slow and less so when the air movement is rapid.

DISCUSSION

DR. A. S. KENNEY, New Orleans: I have had some experience in this line of work over the past three years in Mr. Wells' establishment at the University of Pennsylvania, and I fully appreciate the difficulties attendant on such research. I think this type of work has much more significance in pediatrics than in other branches of medicine because of the advantage in protecting the premature and the small infant from infection. As yet there is no exact information in respect to immediate and distant contact. Mr. Wells assumes that this distant contact is an important factor. You will agree that the immediate contact is important. However, with the increase in the efficiency of air conditioning, the factor of sterilization is going to become more important, since the air must be sterilized to be completely safe. I have had some experience with pathogens. My associates and I found about two years ago in studying the air in the ordinary infant ward that the incidence of pathogens was about one and a half colonies per 5 cubic feet (0.14 meter), whereas the total number of colonies on the culture tubes obtained from 5 cubic feet of air was about five hundred. However, in comparing the results after ultraviolet irradiation of air under normal conditions, we found that the percentage of Streptococcus viridans was considerably reduced. Str. viridans comes from the nasopharynx. It seems likely that under clinical conditions ultraviolet radiation will be effective. From the practical point of view it seems more important to protect the infant from immediate contact. Masks are ineffective. In the care of premature infants the use of incubators which completely isolate the babies is much to be desired.

DR. F. F. TISDALL, Toronto: One can see the great possibility of these studies from the standpoint not only of hospitals but of the whole problem of ventilation today. The General Electric Company of Schenectady has sent one of its physicists to Toronto to collaborate in the construction of these cubicles. One cannot fully evaluate sterilization of the air until it is tried out practically. It will take two or three years to ascertain exactly what its value is. If Dr. Robertson will mention the counts of organisms found in the outpatient department, you will realize the extent of contamination present in the air of many of our hospitals today.

DR. E. CHANT ROBERTSON, Toronto: In the outpatient department there were five hundred to six hundred bacteria per cubic foot.

IMMUNOLOGIC PROPERTIES OF SCARLATINA CONVALESCENT SERUM

ELIZABETH MOORE, M.D.
AND
WILLIAM THALHIMER, M.D.
NEW YORK

Serum from persons convalescent from scarlet fever has been used successfully in the prophylaxis and treatment of patients with this disease.[1] The literature on this subject has been reviewed by Hyland and Anderson.[1c] Apparently the clinical effectiveness of convalescent serum is only partially dependent on its antitoxin content, for such serum in general contains less than 12 units per cubic centimeter.[2] It has been assumed, therefore, that other protective substances in human serum contribute to the therapeutic effectiveness. Several workers have found an increased bactericidal power against hemolytic streptococci in serum obtained from patients with various diseases associated with these organisms. For example, Hare [3] detected in the serum of persons who recovered from puerperal fever an augmented bactericidal action

Aided by a grant from the Nathan Hofheimer Foundation, Inc.

From the Manhattan Convalescent Serum Laboratory and the Bureau of Laboratories, New York City Department of Health.

1. (*a*) Hoyne, A. L.; Levison, S. O., and Thalhimer, W.: Convalescent Scarlet Fever Serum: Its Prophylactic and Therapeutic Value; a Review of 2,875 Cases, J. A. M. A. **105**:783-789 (Sept. 7) 1935. (*b*) McGuinness, A. C.; Stokes, J., Jr., and Mudd, S.: The Clinical Uses of Human Serums Preserved by the Lyophile Process, J. Clin. Investigation **16**:185-196, 1937. (*c*) Hyland, C. M., and Anderson, L. R.: Prophylactic and Therapeutic Use of Scarlet Fever Convalescent Serum, Am. J. Dis. Child. **54**:504-519 (Sept.) 1937. (*d*) Thalhimer, W.: The Use of Convalescent Scarlet Fever and Measles Sera in Prophylaxis and Therapy, Bull. New York Acad. Med. **14**:361-373, 1938. (*e*) Rhoads, P. S.: The Quantitative Nature of Immunity, Illinois M. J. **72**: 503-511, 1937.

2. (*a*) Plummer, H.: The Antitoxin Content of Human Serum in Relation to the Dick Reaction, Tr. Roy. Soc. Canada (Sect. 5) **28**:97-99, 1934. (*b*) Rhoads, P. S., and Gasul, B. M.: Convalescent Scarlet Fever Serum and Commercial Antitoxin, J. A. M. A. **102**:2005-2008 (June 16) 1934.

3. Hare, R.: The Production of Bacteriotropins for Hemolytic Streptococci by Patients Infected with That Organism, J. Path. & Bact. **35**:701-705, 1932; The Hemolytic Streptococci from the Vagina of Febrile and Afebrile Parturient Women, ibid. **38**:129-141, 1934; The Ability of Hemolytic Streptococci Found in Infected Throats to Resist the Bactericidal Power of Normal Human Blood, ibid. **38**:143-144, 1934; Alterations in the Bactericidal Power of the Blood Which Occur During Hemolytic Streptococcal Infections in the Puerperium, ibid. **41**:61-75, 1935.

against hemolytic streptococci isolated from these persons. Fothergill and Lium,[4] also using homologous organisms, demonstrated increased activity in the serums of 2 patients who recovered from scarlet fever accompanied by complications, but in the serums of 2 persons who had scarlet fever without complications they observed no increased bactericidal power. Using another method of approach, Tunnicliff [5] observed that twenty-six different lots of pooled serums from patients with scarlet fever possessed a high opsonic index to streptococcus scarlatinae. Moreover, Hare [6] found that patients suffering from puerperal fever due to the hemolytic streptococcus possessed in their serum a heat-stable opsonin against the homologous organism.

In the present study we have determined the antitoxin content and the bactericidal power of convalescent scarlatina serums which were subsequently pooled and distributed by the Manhattan Convalescent Serum Laboratory for the prophylaxis and treatment of scarlet fever.

METHOD

The amount of streptococcus antitoxin in human serum was estimated by the method of Fraser and Plummer.[7] Standard toxin and antitoxin for use in these tests were obtained from B. S. Kolchin of the bureau of laboratories of the New York City Department of Health and from the National Institute of Health, respectively.

Bactericidal action of serum was determined by a modification of the method of Thalhimer and Colwell:[8] 4 cc. of defibrinated or, in a few cases, heparinized blood, 2 cc. of the serum to be tested and 0.5 cc. of an eighteen hour culture diluted in broth to contain about 2,500 viable hemolytic streptococci per cubic centimeter were mixed in a test tube, which was kept in constant motion in a water bath at 37 C.; 0.5 cc. samples of this mixture were withdrawn immediately and at two, four and six hours; they were added to 15 cc. of melted nutrient agar medium and the mixtures poured into Petri dishes. Samples of each serum to be tested were run in duplicate. The colonies were counted on the plates after incubation overnight at 37 C., and the average count of the two identical samples was used in determining the results. When the growth of bacteria in the test

4. Fothergill, L. D., and Lium, R.: The Value of Commercial Antibacterial Streptococcus Sera in Hemolytic Streptococcus Infections, New England J. Med. **211**:99-101, 1934.

5. Tunnicliff, R.: Opsonins for Diplococcus Morbillorum and for Streptococcus Scarlatinae in Convalescent Measles Serum, Convalescent Scarlet Fever Serum and Placental Extract, J. Infect. Dis. **58**:1-4, 1936.

6. Hare, R.: On the Phagocytosis of Hemolytic Streptococci of High and Low Virulence by the Blood of Patients Infected with That Organism, Brit. J. Exper. Path. **9**:337-352, 1928.

7. Fraser, F. H., and Plummer, H.: The Titration of Scarlatinal Antitoxin by Means of a Skin Test in Chinchilla Rabbits, Brit. J. Exper. Path. **11**:291-297, 1930.

8. Thalhimer, W., and Colwell, C.: A Method for Measuring the Bactericidal Action of Whole Blood Against Gram Positive Cocci, J. Lab. & Clin. Med. **14**:441-450, 1929.

serum mixtures was equal to that in the normal serum mixture, the result was interpreted as negative; a complete or almost complete disappearance of viable organisms from the test serum mixture after incubation for four or six hours was considered evidence of excellent bactericidal power; for gradations between these two extremes the terms "slight" and "moderate" were employed.

Defibrinated normal blood was obtained at the time of the experiment from a donor whose blood was known to have no demonstrable bactericidal power against hemolytic streptococci of the types employed. Moreover, donors were chosen whose erythrocytes were not agglutinated by the test serum. In addition, the normal human serum used in control tests was free from bactericidal action against the test organism.

Four types (Griffith) of hemolytic streptococci belonging to group A (Lancefield) were employed in the present experiments: type 1, a virulent strain designated S. F. 130/2; type 3, a virulent strain of "Lewis opaque" designated 4/1; type 30, a virulent strain designated D53A by R. C. Lancefield and isolated by A. F. Coburn from the throat of a patient with scarlet fever in the winter of 1936 to 1937,[9] and type 10, an avirulent culture of the NY5 strain, in which the M substance appeared to be lacking, according to Lancefield.[10]

The majority of the serums were retested at least once. Thirty-one of the 70 convalescent serums were employed against the avirulent strain of NY5 and one of the virulent strains of group A (Lancefield) hemolytic streptococci in the same experiment. Thus the bactericidal power of most human serums for the NY5 organism was determined three or four times.

Subjects who had recovered from scarlet fever were bled repeatedly from eighteen days to six months after onset of the disease. Serologic studies were made at intervals on 70 serums which were stored without preservative at 5 C. for one and one-half to fourteen months.

RESULTS

Antitoxin Content of Convalescent Serum.—The amounts of antitoxin in 51 convalescent serums, determined by titration of the toxin-serum mixtures in the skin of rabbits, are given in table 1. The antitoxin ranged from less than 1 unit (United States standard) to 10 units per cubic centimeter, and 39 per cent of the serums contained between 2 and 4 units per cubic centimeter. The average value of antitoxin in the 51 samples was 3.3 units per cubic centimeter.

A slight diminution in titer generally occurred in successive samples of serum obtained from one and one-half months to six months after onset of the disease. Two typical instances may be cited: The serum of a patient obtained on the sixty-fourth day contained 2.6 units per cubic centimeter, while a sample taken on the one hundred and eightieth day had 2.2 units. Another patient had 5.8 units per cubic centimeter in serum taken on the forty-seventh day, while 4.2 units were found on the one hundred and sixty-eighth day. All antitoxin titrations were made on serum which had been stored from four to nine months.

9. Virulent strains of types 1, 3 and 30 were dried from the frozen state by R. C. Lancefield and supplied to us.

10. Lancefield, R. C.: Personal communication to the authors.

Bactericidal Power of Convalescent Serum.—Sufficient evidence [11] has accumulated to indicate that although a number of types of group A streptococci can be isolated from the throats of patients with scarlet fever in individual epidemics, nevertheless one or two types generally predominate. Green [11a] isolated eight serologic types (Griffith) of hemolytic streptococci from the throats of patients in an epidemic of scarlet fever in 1933. For several months before the epidemic and early in the epidemic type 5 predominated, while as the epidemic progressed type 3 became the most common. Furthermore, the distribution of predominant types of streptococci in epidemics of scarlet fever appears to vary according to the geographic locality. Bailey [11b] observed that of 243 cases of scarlet fever and scarlatinoid angina typed in 1936 in Chicago, 70 per cent fell into groups in which the streptococci were determined to be of types 2, 3 or 6. White and his associates [11c] found that during two epidemics of scarlet fever in Australia the strains isolated were of fifteen types with a predominance of those of types 11 and 17. Keogh [11d] observed that types 2 and 17 were most frequently found in another group examined in Australia. In England four serologic types, viz., 1, 2, 3 and 4, are most commonly found in patients with scarlet fever.[11e]

TABLE 1.—*Antitoxin Content of Fifty-One Convalescent Scarlet Fever Serums*

Units of antitoxin per cubic centimeters	1	1 to 2	2 to 4	4 to 6	6 to 8	8 to 10
Number of serums	1	14	20	9	6	1

Since type specificity is characteristic of certain antibodies which develop against organisms of group A, i. e., anti-M precipitins,[12] protective antibodies [12] and opsonins,[13] an investigation of the bactericidal

11. (*a*) Green, C. A.: The Serological Types of Hemolytic Streptococci in Epidemic Scarlatina, J. Hyg. **37**:318-331, 1937. (*b*) Bailey, J. H.: The Types of Hemolytic Streptococci Concerned with Scarlet Fever and Scarlatinoid Angina, J. Bact. **31**:80-81, 1936. (*c*) White, C.; Rudd, G. V., and Ward, H. K.: The Serological Types of Hemolytic Streptococci Causing Scarlet Fever in Sydney, M. J. Australia **1**:96-100, 1939. (*d*) Keogh, E. K.: Observations on the Epidemiology of Streptococcal Infections, ibid. **1**:100-103, 1939. (*e*) Allison, V. D.: Streptococcal Infections, Lancet **1**:1067-1070, 1938.

12. Lancefield, R. C.: The Antigenic Complex of Streptococcus Hemolyticus: I. Demonstration of a Type-Specific Substance in Extracts of Streptococcus Hemolyticus, J. Exper. Med. **47**:91-103, 1928.

13. Mudd, S.; Czarnetzky, E. J.; Lackman, D., and Pettit, H.: The Antigenic Structure of Hemolytic Streptococci of Lancefield Group A: I. The Preparation of a Labile, Type-Specific Antigen; Its Identification as the Griffith Type-Specific Agglutinogen and as a Substance from Which a Group-Specific and a Type-Specific Hapten Are Derivable, J. Immunol. **34**:117-153, 1938.

action of convalescent scarlatina serum should include studies with a number of types of the group. Accordingly, we have used cultures of four types of group A streptococci in our investigation. Sixty-seven serums were tested against the NY5 strain, of which 49 (73 per cent) gave positive results and 29 (43 per cent) negative. Thirty-six of these serums were tested against the NY5 strain alone, while 31 were also

TABLE 2.—*Comparison of Serums from Patients Convalescent from Scarlet Fever with Respect to Bactericidal Effect on Different Types of Group A Streptococci*

	Antibody Reaction with Given Type of Streptococcus			
Serum	Type 10 NY5	Type 3	Type 1	Type 30 D53A
1	++	0	0	0
2	+++	..	+++	..
3	+	..	..	0
4	++	..	0	0
5	++	..	0	0
6	++	..	++	0
7	++	+	0	0
8	0	..	0	0
9	++	++	0	0
10	0	..	..	0
11	..	..	..	0
12	0	0	0	0
13	0	..	+	0
14	+	..	0	0
15	0	..	..	0
16	..	..	..	0
17	++	..	0	0
18	0	+	0	0
19	0	..	+	0
20	0	+	0	0
21	+++	..	..	0
22	+	..	+	0
23	+	..	..	0
24	+	0	..	..
25	0	..	0	0
26	..	..	..	0
27	++	0	..	0
28	0	..	..	0
29	+	..	..	0
30	++	++	..	0
31	+++	0	..	+
32	+++	++	..	..
33	+	0	0	0
34	0	0	0	0
Number of serums tested	31	13	19	31
Number giving positive reactions	20	6	5	1
Percentage giving positive reactions	64.5	46.1	26.3	3.2

+++ signifies that bactericidal power is good; ++, moderate; +, slight, and 0, absent.

used with three virulent strains. The combined results with these 31 serums and 3 additional serums are summarized in table 2. In this subgroup 64.5 per cent of the specimens had some bactericidal effect on the NY5 streptococcus. Antibodies against type 3 streptococci, found in 46.1 per cent of 13 serums, were the next most common. Some bactericidal effect on the type 1 organism was displayed by 26.3 per cent of the serums, but only 1 serum had any effect on the type 30 streptococcus. Not a single specimen in the entire subgroup of 34 serums

was capable of killing bacteria of all four types tested, and, moreover, 9 of them had no apparent effect on any of the types.

Eight serums were each effective against two types. These polyvalent serums always destroyed the NY5 strain and one of the virulent strains, but none showed bactericidal action against more than one virulent type. Twelve members of the group summarized in table 2 acted only against the NY5 strain, while 4 had effect on one of the other types but not on NY5. If the tests with virulent strains of types 1, 3 and 30 are considered as a unit, 74 per cent of the serums possessed antibodies for one or another of the three types.

Serums taken from 2 patients six months after onset of the disease possessed about the same bactericidal power as did samples obtained two and three months after onset. In another case a specimen drawn three months after onset possessed excellent bactericidal activity, but the one obtained six months after onset was devoid of these substances. Storage

TABLE 3.—*Summary of Studies on Bactericidal Action of Convalescent Serum*

	Serums Giving Positive Reactions with One or More of Types of Group A Hemolytic Streptococci Tested		Serums Giving Positive Reactions with None of Types of Group A Hemolytic Streptococci Tested	
Serums Tested	Number	Percentage	Number	Percentage
70	42	60	28	40

at 5 C. without preservative appeared to exert little deleterious effect on the bactericidins, since serum retained its activity for fourteen months when kept under these conditions.

A summary of all determinations of the bactericidal activity of convalescent serum is given in table 3. Seventy serums were studied with one or more of the types of streptococci. Forty-two (60 per cent) of this group showed a demonstrable effect on one or more of the types. Twenty-eight (40 per cent) failed to react with any of the strains tested.

COMMENT

Our observations on the streptococcus antitoxin content of 51 serums from patients convalescent from scarlet fever indicate that this antibody is generally present in amounts of less than 10 units per cubic centimeter (United States standard), which is in agreement with the findings of others (Rhoads;[1e] Plummer;[2a] Rhoads and Gasul[2b]). Rhoads[1e] apparently assumed that the beneficial therapeutic effects of convalescent serum were dependent solely on the antitoxin content of the serum and as a result believed that serum is rarely given in adequate doses. It is not the purpose of this communication to enter into a clinical discussion

of dosage but rather to point out that immune substances other than antitoxin are present in convalescent serum in demonstrable amounts and may contribute to the effectiveness of the serum.

The present observations indicate that the bactericidal substances which appear in the serum of patients after an attack of scarlet fever are type-specific in their action on virulent hemolytic streptococci. Thus, 25 of 34 serums (74 per cent) acted on one or another of the three virulent types of streptococci employed, but no serum had effect on more than one. On the other hand, 8 of the 20 serums (40 per cent) which reacted with the avirulent NY5 strain were also active against one or another of the three virulent strains. Evidence is insufficient to offer an explanation for the greater incidence of bactericidins against the NY5 strain. It should be borne in mind that this strain, apparently because of its lack of M substance, gives many cross reactions as well as certain type-specific reactions.[10]

It has been our custom to pool lots of serum obtained from 30 to 40 patients who have recently recovered from scarlet fever before dispensing convalescent serum for clinical use. This empirical procedure, which has given successful clinical results, now has experimental evidence to warrant its continuation. Since several types of hemolytic streptococci are encountered in each epidemic, the chance of including the proper type-specific antibodies for the less frequently occurring organisms is small unless a number of serums for each type are present in the pool. On the other hand, it is probable that a pool made up of serums collected from patients in a given epidemic will contain many antibodies against the types of hemolytic streptococci most commonly encountered in that epidemic. For this reason it is important that convalescent serum be collected early in the epidemic, pooled and used for therapeutic purposes while the organisms against which the antibodies have been elaborated are still predominant. All these difficulties would be obviated were it the general practice in hospitals to type the streptococcus responsible for the infection, just as is done in the diagnosis and treatment of pneumonia due to the pneumococcus. Antiserums for each type of streptococci could be pooled and used for the treatment of patients with infections caused by the corresponding type of organism. Lyons [14] suggested that a somewhat similar procedure be used in treating patients with hemolytic streptococcic infections other than scarlet fever by transfusion from donors with a high specific antibacterial immunity as determined by the opsonin method.

It is of considerable importance to know how long antistreptococcus immune substances persist in the blood of patients after infection and

14. Lyons, C.: Immunotransfusion and Antitoxin Therapy in Hemolytic Streptococcus Infections, J. A. M. A. **105**:1972-1975 (Dec. 14) 1935.

how well these substances withstand storage, for a serum center must obtain large amounts of convalescent blood and must maintain a considerable reserve stock. Our observations indicate that both antitoxic and bactericidal substances against hemolytic streptococci generally persist in patients' serum for at least six months after onset of scarlet fever and that these properties of serum are not lost after storage in the cold for considerable periods. The persistence of bactericidal substances in the serum of our patients with scarlatina, as well as the relative specificity of these substances, would appear to differentiate them from the nonspecific bactericidal agents present during acute infections.[15]

CONCLUSIONS

The serum of patients convalescent from scarlet fever contains bactericidal substances and antitoxin which react with hemolytic streptococci and their products. These immune substances persist in the blood of many patients for six months after onset of scarlet fever, and they remain active for at least nine months in samples of convalescent serum which have been stored.

Bactericidal substances which appear in the serum of patients who have recovered from scarlet fever are type-specific in their action on hemolytic streptococci of group A (Lancefield).

In order to obtain a polyvalent serum for the treatment of scarlet fever and streptococcic infections, it appears advisable to pool specimens of serum taken from a large number of patients recently recovered from scarlet fever.

---

15. Tillett, W. S.: The Bactericidal Action of Human Serum on Hemolytic Streptococci: I. Observations Made with Serum from Patients with Acute Infections and from Normal Individuals, J. Exper. Med. **65**:147-161, 1937.

Case Reports

TANNING FROM ULTRAVIOLET IRRADIATION BROUGHT OUT BY BLOOD TRANSFUSION

E. O. JODAR, M.D.
DETROIT

While it is well known that pigmentation of the skin, or tanning, results from ultraviolet irradiation with a mercury vapor lamp and that different persons vary in their susceptibility to the effects produced, the exact mechanism of this process has as yet not been satisfactorily explained. This report suggests that ultraviolet irradiation may at times sensitize the cells of the skin so that tanning is produced only when the necessary products for pigment formation are supplied by the blood of a normal person.

Mayer [1] presented this theory of pigment formation: ". . . pigment, as we see it in the skin, is the product of the reaction of an enzyme contained in the epithelial cells, and a colorless chromogen which is very closely related chemically to dioxyphenylalanin ('dopa') if not identical with it. . . . Local pigmentation probably results only when there is some degree of hyperemia and associated damage to the cells, with the subsequent formation of 'dopa' as a by product of cellular autolysis." Laurens [2] stated that the amino acids, tyrosine and phenylalanine are present in human blood as the source of pigment. The enzymes tyrosinase and dopa oxidase act on their respective amino acids, forming red, brown or black pigment of melanin or "dopa melanin." This action takes place in the epidermis, and the pigment is phagocytosed by the connective tissue cells (chromatophores) and deposited in the dermal layer. "In the action of various radiations on the pigment-producing ferments of the skin, Lutz (1917) observed an influence only where the oxidase is manifestly or latently present." To emphasize the idea that the oxidase may remain latent for some time and that the "by product of cellular autolysis" may not be carried away promptly the following case report is presented:

REPORT OF A CASE

C. S., a boy of 9½ months, was referred to me by another physician, who because of the child's extreme pallor thought that a blood transfusion was needed.

1. Mayer, E.: Clinical Applications of Sunlight and Artificial Radiation, Baltimore, Williams & Wilkins Company, 1926.

2. Laurens, H.: The Physiological Effects of Radiant Energy, American Chemical Society Monograph, New York, Chemical Catalog Company, Inc., 1933.

The boy was delivered spontaneously at term, weighing 6 pounds and 2 ounces (2,778 Gm.). On the second day after birth he was circumcised, after which he bled profusely. At that time he was given one intramuscular injection of whole blood. He was breast fed, and administration of solid foods and cod liver oil with viosterol was started at an early age. No teeth were present, and the child did not stand, although he could sit without support. The only illness had been one mild "cold." Because of his apparent anemia the infant had been given two kinds of iron tonic, the nature of which was not known. He had also been given eighteen treatments with a mercury vapor lamp in a physician's office at intervals of one week.

On physical examination he was found to have a very pale, rather yellow skin. The nutrition was poor, the weight being 15 pounds and 7 ounces (7,002 Gm.). The mucous membrane of the mouth was extremely pale. The throat seemed redder than normal, and the cervical glands were distinctly palpable. There was a loud systolic murmur over the entire cardiac area. The abdomen was prominent. Other physical features were normal.

The results of the blood studies made at this time are shown in the first line of the tabulation.

Day of Observation	Hemoglobin, Gm.	Red Blood Cells	White Blood Cells
First	6	3,160,000	8,000
Second	10.6	4,600,000	19,600
Twenty-first	13	5,440,000	

When the blood cells of the patient and his mother were grouped, they were found to fall into Landsteiner's O (Moss IV), and by direct matching the mother was found to be a compatible donor.

The patient was given 180 cc. of citrated blood from the mother. This therapy was followed two hours later by a moderate reaction consisting of rather rapid and distressed breathing and an elevation of temperature from a normal level to 101.8 F. (rectal). This was relieved by a cool sponge bath, an alcohol rub and 2 grains (0.13 Gm.) of acetylsalicylic acid, so that the child slept throughout the night. The next morning the mother reported that the child's skin was exceedingly yellow. When I closely examined the infant, I determined that instead of the yellow color of jaundice, which was anticipated, the skin had a light tan color. I further noted that there was a light area around each eye which corresponded exactly with goggles which the child wore when he received the ultraviolet irradiation. Examination of the blood at this time gave the results shown in the second line of the tabulation. On a smear it was noted that some of the red cells appeared pale, while others had a distinctly deeper stain.

The patient was given 9 grains (0.58 Gm.) of iron and ammonium citrates daily. After nineteen days he had gained 15 ounces (425 Gm.), and the condition of the blood had improved, as can be seen in the third line of the tabulation. At this time the skin had a normally pink color, and there was no evidence of tanning.

This report suggests that the lack of the precursors of pigment (tyrosine and phenylalanine) in the blood in quantities sufficient to allow for the usual tanning by ultraviolet irradiation is entirely com-

patible with life. It strongly suggests that the cells can be sensitized by ultraviolet irradiation and that the pigment-producing enzymes can be activated and can remain present in latent form so that when the necessary products (probably the amino acids tyrosine and phenylalanine) are supplied by the blood of a normal person the process of tanning occurs quickly.

5005 Bedford Road.

ANEMIA OF NEWBORN IN ONE IDENTICAL TWIN AND UNIVERSAL EDEMA OF NEWBORN IN THE OTHER

WITH SURVIVAL IN BOTH CASES

LAWRENCE M. SHAPIRO, M.D.
AND
PHILIP COHEN, M.D.
NEW YORK

During the past decade there has been a tremendous spurt in interest, reflected by increasing numbers of reports in the literature, concerning universal edema of the newborn, icterus gravis and anemia of the newborn. With this increased interest the concept has emerged that these three different clinical pictures are actually manifestations of the same disease process.

The cases which we are presenting in this report we believe to be of great significance. In regard to severity they represent the opposite extremes of the related group included in so-called erythroblastosis fetalis. These widely divergent clinical pictures occurred in identical twins after the mother had given birth to seven normal children. At the time of writing, both children are over 1 year of age, a situation unique in the literature on this subject, for it has been universally stated that infants with congenital hydrops who are not born dead always perish shortly after birth. For this very reason the exhibit on erythroblastosis fetalis displayed at the New York Academy of Medicine from Oct. 24 to Nov. 4, 1938, during the fortnight on diseases of the blood and blood-forming organs, emphasized that hematologic data on congenital hydrops were practically nil. We are able to present a hematologic investigation which included aspiration of sternal bone marrow.

It is not our purpose to review the extensive literature on this subject, for we feel that nothing could be added to the reports of such writers as Abt,[1] Diamond, Blackfan and Baty,[2] Pasachoff and Wilson,[3]

From the Pediatric Service of Dr. Herman Schwarz, Beth Israel Hospital.

1. Abt, A. F.: Anemia of the New-Born, Am. J. Dis. Child. **43**:337 (Feb.) 1932; J. Pediat. **3**:7, 1933.

2. Diamond, L. K.; Blackfan, K. D., and Baty, J. M.: J. Pediat. **1**:269, 1932.

3. Pasachoff, H. D., and Wilson, L.: Congenital Anemia of the New-Born: Necropsy and Review of the Literature, Am. J. Dis. Child. **42**:111 (July) 1931.

Peters,[4] Hawksley and Lightwood,[5] Abbott and Abbott [6] and Astrachan.[7] However, we offer for appraisal certain important historical data to show the relationship to be a real one among the three members of the triad, namely, universal edema of the newborn, icterus gravis and anemia of the newborn. Before doing so, however, it is necessary to clarify two terms:

1. Erythroblastosis means widespread extramedullary hemopoiesis, chiefly in the liver and spleen; it can be recognized only by histologic examination of the organs.

2. Erythroblastemia means the presence in the peripheral circulation of a larger number of nucleated red blood cells than the physiologic maximum for the age.

Buchan and Comrie [8] in 1909 were the first to note the significance of widespread marked extramedullary hemopoiesis as the underlying pathologic condition in icterus gravis. Schridde [9] in 1910 first emphasized that hydrops foetalis with erythroblastosis is a definite clinical and pathologic entity, as opposed to widespread edema in the newborn due to other causes. This entity is now known as the Schridde type of universal edema of the newborn.

In 1912 Rautmann [10] gave the name erythroblastosis to the underlying pathologic condition present in the Schridde type of hydrops. Von Gierke [11] in 1921, noting in a case of icterus gravis with kernicterus a pathologic picture similar to that described by Schridde, established the hypothesis that these diseases may be related. He was also impressed by the occurrence in the same family of each of these conditions. Several cases of both entities occurring in the same family have been reported before and after his observations.[12] Moreover,

4. Peters, R.: Beitr. z. path. Anat. u. z. allg. Path. **92**:531, 1934.

5. Hawksley, J. C., and Lightwood, R.: Quart. J. Med. **27**:155, 1934.

6. Abbott, K. H., and Abbott, F. F.: Idiopathic Anemia of the New-Born: Review of the Literature and Report of Two Cases, Am. J. Dis. Child. **49**:724 (March) 1935.

7. Astrachan, M.: Jaundice in Children: Report of Six Cases of Icterus Gravis Neonatorum, Am. J. Dis. Child. **53**:137 (Jan., pt. 1); 541 (Feb.) 1937.

8. Buchan, A. H., and Comrie, J. D.: J. Path. & Bact. **13**:398, 1909.

9. Schridde, H.: München. med. Wchnschr. **51**:397, 1910.

10. Rautmann, H.: Beitr. z. path. Anat. u. z. allg. Path. **54**:332, 1912.

11. von Gierke, E. V.: Verhandl. d. deutsch. path. Gesellsch. **18**:322, 1921.

12. (*a*) Ballantyne, J. W.: Manual of Antenatal Pathology and Hygiene: The Foetus, Edinburgh, W. Green & Sons, 1902. (*b*) Bock, A.: Ztschr. f. Geburtsh. u. Gynäk. **97**:257, 1930; cited by Peters.[4] (*c*) de Groot, J.: Nederl. tijdschr. v. verlosk. en gynaec. **32**:274, 1927; cited by Diamond, Blackfan and Baty.[2] (*d*) Hubbard, J. C.: Boston M. & S. J. **168**:459, 1913. (*e*) King, W. W.: Lancet **2**:532, 1908. (*f*) Kratzeisen, E., and Ballhorn, W.: Ztschr. f. Kinderh. **39**:314, 1925; cited by Peters.[4] (*g*) de Lange, C.: Acta pædiat. **13**:292, 1932. (*h*) Plaut,

(Footnote continued on next page)

there have been reports of cases [13] in which icterus and edema were present in the same patient at the same time.[14] The evidence which established the unquestioned relation between the Schridde type of congenital hydrops and icterus gravis was first supplied in 1927 by Plaut,[12l] who described a case of hydrops and one of icterus gravis in children of the same parents. Plaut observed the same underlying pathologic picture in both infants, namely, marked widespread extramedullary hemopoiesis.

Ecklin's report,[15] published in 1919, is generally credited with giving the first description of anemia of the newborn as a clinical entity. As evidence that anemia of the newborn and icterus gravis are related, the following facts may be adduced: Buchan and Comrie [8] in 1909 had emphasized the presence of severe anemia in 4 cases of icterus gravis. In cases of anemia of the newborn, jaundice is a not uncommon clinical finding.[16] Furthermore, there have been reports in the literature [17] of the occurrence of icterus gravis and anemia of the newborn in siblings. Diamond, Blackfan and Baty in 1932, citing their own experience and that of others,[18] pointed out that after a few weeks a surviving patient with icterus gravis is likely to show the same clinical and hematologic picture as seen in anemia of the newborn shortly after birth.

These authors stated the belief that since hydrops and icterus gravis are related and since icterus gravis and anemia of the newborn are related, therefore hydrops and anemia of the newborn are related. This contention was upheld in 1935 by Pasachoff and Wilson,[19] who reported on siblings, 1 of whom had anemia of the newborn and 2 of whom

---

A., and Bullard, E. A.: Arch. Pediat. **43**:292, 1926. (*i*) Plaut, A.: Erythroblastosis, "Kernicterus," and Congenital Hydrops, Arch. Path. **4**:137 (July) 1927. (*j*) Salomonsen, L.: Ztschr. f. Kinderh. **51**:181, 1931. (*k*) Stork, F.: Zentralbl. f. Gynäk. **57**:425, 1933; cited by Peters.[4] (*l*) Diamond, Blackfan and Baty.[2] (*m*) Peters.[4]

13. Eichelbaum, H. R.: Arch. f. Gynäk. **119**:149, 1923; cited by Peters.[4] Runge, H.: Inaug. Dissert., Heidelberg, 1933; cited by Peters.[4] Diamond, Blackfan and Baty.[2] Kratzeisen and Ballhorn.[12f] Peters.[4]

14. In some cases of severe icterus gravis we have seen pathologic sections which revealed fairly widespread edema, not suspected clinically.

15. Ecklin, T.: Monatschr. f. Kinderh. **15**:425, 1919.

16. Gregory, H. C.: Proc. Roy. Soc. Med. **21**:1730, 1928. Susstrunk, G.: Ztschr. f. Kinderh. **38**:586, 1924. Abbott and Abbott.[6] Diamond, Blackfan and Baty.[2] Ecklin.[15] Pasachoff and Wilson.[8]

17. Diamond, Blackfan and Baty.[2] Ecklin.[15]

18. Buchan and Comrie.[8] Diamond, Blackfan and Baty.[2]

19. Pasachoff, H. D., and Wilson, L.: Association of Universal Edema of the Fetus and Congenital Anemia of the Newborn, Am. J. Dis. Child. **49**:411 (Feb.) 1935.

had hydrops. The present report seems strongly to confirm this argument, for of the identical twins we present one had hydrops and the other anemia of the newborn. And, interestingly enough, after the age of 5½ weeks the twin with the hydrops presented an anemic picture identical with that of his brother.

REPORT OF CASES

S. H. and M. H., twin boys, were born on Oct. 9, 1937. They were the eighth and the ninth child, respectively.

The father, aged 41, had gastric ulcers for many years. The mother, aged 37, was robust but had been "troubled with heart trouble" which was unconfirmed by clinical, roentgen and electrocardiographic examinations at the cardiac clinic. Both parents were Austrian by birth, but careful questioning of parents and grandparents revealed that there had been no intermarriage as far back as could be remembered. Both families were characterized by longevity, and there were no known cases of diseases of the blood or of the blood-forming organs.

All of the other children of these parents were living and well. They were normal at birth and were delivered at term in maternity hospitals, and each had weighed over 8 pounds (3,629 Gm.). There had been no miscarriages. In chronologic order, the children were three girls, aged 18, 17 and 15, three boys, aged 14, 10 and 5, and a girl aged 3.

The first day of the mother's last menstrual period was February 10. Thus the date of birth was five and a half weeks earlier than the calculated date of confinement. Unlike her previous pregnancies, this one caused the mother great distress. She vomited frequently and much during the first three months. Nausea and anorexia persisted throughout, and spells of fainting and weakness were constant during the latter half of pregnancy. At about 6 months twin fetuses were suspected, but roentgenograms were not taken until shortly before confinement.

The first stage of labor began at 1 p. m. and the second stage at 3:45 p. m. The first infant, weighing 5 pounds and 5 ounces (2,410 Gm.), was delivered at 4:42 p. m., the membranes having ruptured spontaneously. The second boy was delivered immediately, after artificial rupture of the membranes. His weight was 6 pounds and 14 ounces (3,118 Gm.).

Yellowish discoloration of the amniotic fluid was not noted, nor was either infant covered with suggestive golden-yellow vernix caseosa.[20]

The single placenta was not larger than is normally the case with twin births and had a double amniotic sac. Gross examination by the pathologist revealed no abnormalities of the placenta. Microscopic sections were not made.

S. H., hereafter referred to as twin 1, presented the appearance of a normal newborn child.

However M. H., hereafter referred to as twin 2, presented a picture in startling contrast (fig. 1). For immediately apparent was marked widespread edema of the entire body. Slight pressure with the finger left a deep impression in the skin which lasted many minutes; the scrotum was markedly swollen and edematous; through the tense, pitting wall of the abdomen the liver was barely palpable, but the spleen was not felt. However, in spite of the tremendous edema, the child did not appear gravely ill.

20. Clifford, S. H., and Hertig, A. T.: New England J. Med. **207**:105, 1932. de Lange, C., and Arntzenius, A.: Jahrb. f. Kinderh. **124**:1, 1929.

A diagnosis of congenital hydrops with erythroblastosis was made, and a blood count was ordered. There were 2,600,000 red cells, and the hemoglobin content was 56 per cent. There were 13,790 white cells, the differential count showing neutrophilic predominance, 2 per cent myeloblasts and 7 per cent myelocytes. The erythrocytes showed anisocytosis, especially macrocytosis, polychromasia and poikilocytosis. There were 728 nucleated red cells per 200 white cells, or 50,210 per cubic millimeter.[21]

That night the child was given his first and only transfusion, 50 cc. of citrated blood from his father being injected.

Blood counts [22] were made daily for both children from October 11, when they were 2 days old, through October 19, when they were 10 days of age, and then

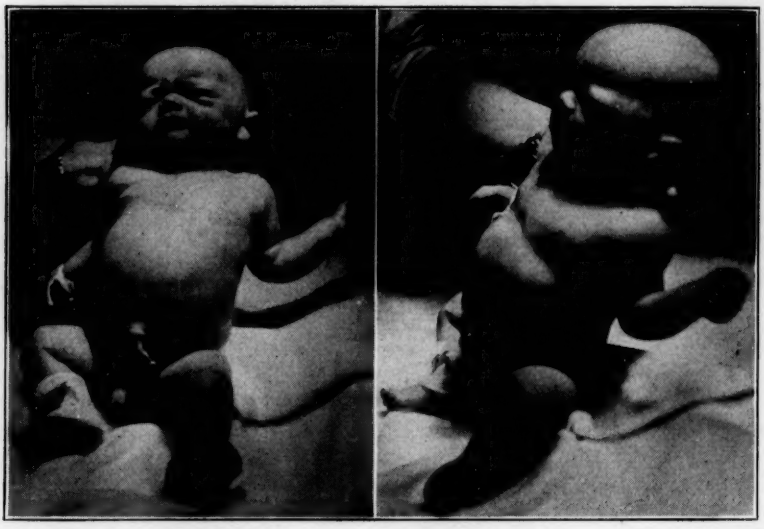


Fig. 1.—Twin 2, nineteen hours after birth.

---

21. In the majority of full term normal infants the nucleated red cells average 1 to 1.5 per hundred white cells during the first day of life, although there may be as many as 24 per hundred white cells. Disappearing rapidly, they are rarely seen by the fifth day (Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, p. 930).

22. The diluent used in counting the red cells and platelets was a 3.8 per cent solution of sodium citrate. The diluent used in counting the nucleated cells in the peripheral blood and in the aspirated bone marrow was a 2 per cent solution of acetic acid. The hemoglobin content was determined by the method of Sahli (100 per cent = 14.5 Gm.).

Cells were examined microscopically in spreads made on glass slides, stained with Jenner and Giemsa stains.

For the differential count of the white cells and the enumeration of the nucleated red cells in the peripheral blood 200 leukocytes were counted. The white cell differential count was expressed in percentage, and the number of nucleated red cells per 200 white cells was estimated. The absolute number of white cells was cal-

(Footnote continued on next page)

TABLE 1.—*Blood Counts for Twin 1**

Date	RBC, Millions	Hgb. %	Hgb. Gm.	Ret., %	WBC	MB, %	MC, %	NS, %	Seg., %	Eo., %	Ba., %	Lym., %	Mon., %	N/200 WBC	Abs. No. N. RBC
1937															
10/11	3.08	90	13.1	3.2	10,710	...	2.0	14.5	48.0	2.0	0.5	27.0	6.0	24	1,290
10/12	3.37	80	11.6	...	5,390	...	4.5	18.5	31.0	8.5	...	26.5	11.0	9	110
10/13	3.66	80	11.6	...	4,620	...	2.5	26.0	19.5	7.5	0.5	31.0	13.0	8	180
10/14	3.65	77	11.2	...	9,180	...	3.5	15.5	6.0	5.0	...	64.0	6.0	8	370
10/15	3.73	74	10.7	...	9,610	0.5	2.5	15.0	13.5	3.5	0.5	54.0	10.5	5	240
10/16	3.41	73	10.6	...	10,790	...	2.0	7.0	27.0	2.0	...	48.0	14.0	2	110
10/17	3.32	74	10.7	...	10,550	...	3.0	16.5	7.0	1.0	...	59.5	13.0	1	50
10/18	3.34	73	10.6	...	15,620	...	3.5	19.5	11.5	4.0	2.0	47.0	12.5	1	80
10/19	3.31	75	10.9	...	12,740	0.5	2.0	24.5	23.0	2.5	1.0	39.5	7.0	1	60
10/21	3.06	75	10.9	...	12,400	0.5	1.5	13.0	18.0	4.0	1.0	52.0	10.0	..	...
10/23	3.53	77	11.2	0.2	14,530	...	1.0	11.5	21.0	3.5	0.5	53.5	9.0	1	70
10/25	3.15	74	10.7	0.4	18,410	...	0.5	7.5	18.5	3.5	1.0	54.5	14.5	1	90
10/28	3.10	74	10.7	0.4	13,000	...	...	16.0	19.0	7.0	1.0	61.0	6.0	..	...
11/ 4	2.74	70	10.2	0.7	17,400	...	...	4.0	18.0	2.0	...	49.0	27.0	..	...
11/ 8	3.32	66	9.6	0.2	8,580	...	...	12.0	20.0	...	2.0	40.0	26.0	4	170
11/12	2.57	64	9.3	0.7	11,920	...	...	4.0	20.0	0.5	0.5	66.0	9.0	8	480
11/15	2.50	70	10.2	0.7	20,050	...	1.0	4.5	18.0	2.0	0.5	58.5	15.5	14	1,400
11/17	2.98	68	9.9	2.7	14,810	..	...	1.0	19.0	5.5	0.5	58.0	16.0	6	440
11/19	2.25	62	9.0	1.6	12,990	...	0.5	6.5	27.0	2.0	0.5	56.5	7.0	4	260
11/23	2.25	58	8.4	1.3	14,010	...	...	8.0	32.0	1.0	...	45.5	13.5	2	140
11/26	2.57	60	8.7	3.4	10,200	...	...	3.0	21.0	2.5	1.0	61.0	11.5	2	100
11/29	3.07	60	8.7	3.9	12,790	...	...	1.0	10.5	3.5	0.5	72.0	12.5	1	60
12/ 2	3.44	65	9.4	1.2	11,090	...	...	2.5	13.5	1.5	...	69.5	13.0	1	60
12/ 6	3.22	65	9.4	1.7	19,350	..	...	7.5	31.0	1.0	0.5	48.5	11.5	..	...
12/ 9	2.83	66	9.6	1.2	10,800	...	...	4.0	21.0	3.5	1.0	62.0	8.5	..	...
12/31	3.98	64	9.3	1.0	15,050	...	...	5.5	20.0	1.0	0.5	57.0	16.0	..	...
1938															
2/ 5	3.79	66	9.6	0.4	10,850	...	...	4.0	23.5	1.0	0.5	61.0	7.0	..	...
3/12	4.19	74	10.7	0.1	7,200	...	...	7.0	11.5	1.0	...	77.5	3.0	..	...
4/11	4.51	78	11.3	0.3	10,350	...	...	4.0	12.0	3.0	...	77.0	4.0	..	...
6/23	4.60	80	11.6	0.2	8,600	...	...	2.5	29.5	0.5	0.5	65.0	2.0	..	...
10/18	4.21	60	8.7	0.2	8,600	...	...	....	38.5	1.0	...	57.5	3.0	..	...

* RBC indicates red cells; Hgb., hemoglobin; Ret., reticulocytes; WBC, white cells; MB, myeloblasts; MC, myelocytes; NS, nonsegmented neutrophils; Seg., segmented neutrophils; Eo., Eosinophils; Ba., Basophils; Lym., lymphocytes; Mon., monocytes; N/200 WBC, nucleated red cells per 200 white cells; Abs. No. N. RBC, absolute number of nucleated red cells.

TABLE 2.—*Blood Counts for Twin 2**

Date	RBC, Millions	Hgb. %	Hgb. Gm.	Ret., %	WBC	MB, %	MC, %	NS, %	Seg., %	Eo., %	Ba., %	Lym., %	Mon., %	N/200 WBC	Abs. No. N. RBC
1937															
10/ 9	2.60	56	8.1	...	13,790	2.0	7.0	19.0	32.0	6.0	...	26.0	8.0	728	50,210
10/11	2.91	68	9.9	10.1	12,210	2.5	9.0	34.0	30.0	1.0	...	20.5	3.0	320	19,540
10/12	3.82	85	12.3	...	6,970	2.5	5.0	14.5	31.5	6.0	1.0	36.5	3.0	319	9,130
10/13	5.04	95	13.8	...	7,070	...	3.0	15.0	35.5	5.5	...	36.0	5.0	237	8,380
10/14	4.91	96	14.2	...	6,890	0.5	3.0	24.0	40.5	5.0	...	17.5	9.5	98	3,210
10/15	4.05	94	13.6	...	7,290	0.5	1.0	15.5	31.5	3.5	1.5	32.0	14.5	21	760
10/16	4.41	95	13.8	...	11,120	0.5	1.0	19.5	11.0	3.0	0.5	55.0	9.5	6	330
10/17	4.24	94	13.6	...	8,560	...	0.5	6.0	20.5	4.0	0.5	57.0	11.5	7	300
10/18	4.87	95	13.8	...	10,800	...	1.0	16.5	21.5	2.0	0.5	40.0	18.5	1	50
10/19	4.42	96	13.9	...	13,780	...	1.5	20.5	15.5	0.5	1.5	49.0	11.5	1	70
10/21	4.03	95	13.8	...	12,400	...	...	15.0	15.0	1.0	...	63.0	6.0	..	...
10/23	4.60	96	13.9	0.5	16,420	...	0.5	10.5	16.0	3.0	0.5	59.0	10.5	1	80
10/25	4.58	100	14.5	0.2	15,650	...	0.5	10.0	17.5	3.0	0.5	52.5	16.0	..	...
10/28	4.49	98	14.2	0.3	15,230	...	1.0	11.0	14.0	2.5	0.5	52.0	19.0	1	70
11/ 4	4.15	84	12.2	0.2	13,900	...	...	4.0	10.0	2.0	1.0	66.0	17.0	..	...
11/ 8	3.12	80	11.6	0.4	10,800	...	...	6.0	32.0	1.0	...	48.0	13.0	..	...
11/12	3.18	74	10.7	0.6	11,900	...	...	4.5	16.0	1.0	2.0	57.0	19.5	..	...
11/15	2.61	70	10.2	1.4	11,320	...	0.5	7.5	25.5	0.5	0.5	47.0	18.5	4	130
11/17	2.97	68	9.9	0.6	17,130	...	...	2.5	18.0	3.0	0.5	66.5	9.5	2	170
11/19	2.44	62	9.0	0.5	15,450	...	...	3.0	24.0	4.5	...	50.0	8.5	2	150
11/23	2.38	58	8.4	2.5	10,050	...	...	6.0	20.0	1.0	1.0	61.0	11.0	4	200
11/26	2.38	62	9.0	0.9	10,390	...	...	1.5	21.0	5.5	0.5	58.0	13.5	6	310
11/29	2.59	60	8.7	1.6	11,840	...	...	2.0	16.0	6.0	1.5	60.0	14.5	6	360
12/ 2	2.75	64	9.3	1.2	13,030	...	...	3.0	17.0	2.5	...	67.5	10.0	1	70
12/ 6	2.90	68	9.9	0.4	13,150	...	...	2.0	24.5	1.0	...	58.5	14.0	..	...
12/ 9	2.77	64	9.3	0.7	14,200	...	...	10.0	53.0	1.5	...	24.5	11.0	..	...
12/31	3.83	58	8.4	0.6	22,150	...	...	8.0	32.0	1.0	...	42.0	17.0	..	...
1938															
2/ 5	3.10	62	9.0	0.2	12,750	...	...	3.0	20.0	2.0	...	67.0	8.0	..	...
3/ 2	4.33	74	10.7	0.4	14,700	...	...	3.0	16.0	1.0	1.0	71.0	8.0	..	...
4/11	4.92	78	11.3	0.6	9,700	...	...	5.0	18.0	1.0	...	74.0	2.0	..	...
6/23	4.65	76	11.0	0.2	16,100	...	...	5.0	35.0	0.5	1.0	54.5	4.0	..	...
10/18	4.19	56	8.1	0.1	11,200	...	...	2.0	41.0	...	1.0	43.0	13.0	..	...

* See footnote to table 1.

at longer intervals as improvement continued, during their hospital stay as well as in the follow-up clinic (tables 1 and 2). Other laboratory examinations were also made (table 3).

We shall now follow the significant data on twin 2 (fig. 2).

The edema was marked for a few days and then began to diminish, disappearing completely after two weeks.

Despite adequate diet and good appetite the weight dropped gradually from 6 pounds and 14 ounces (3,118 Gm.) until it reached the low point of 4 pounds and 8½ ounces (2,055 Gm.), at 2 weeks; it began to rise the next day, when for the first time the edema was noted to be absent.

The liver remained palpable until the age of 3½ weeks.

The spleen was never palpable.

TABLE 3.—*Other Laboratory Data*

	Twin 1
Bone marrow (obtained by aspiration)	10/12: 73,700 nucleated cells per cu. mm., 2.6% myeloblasts, 22.0% neutrophilic myelocytes, 1.8% eosinophilic myelocytes, 20.8% nonsegmented neutrophils, 4.0% segmented neutrophils, 2.0% eosinophils, 9.4% lymphocytes, 2.6% hematogones, 34.8% nucleated red cells
Platelets	10/11: 170,000; 11/4: 380,000
Urine	10/11 and 10/13: completely normal
Icterus index	10/16: 44.0; 10/26: 13.7
Van den Bergh reaction	10/16: biphasic (7.5 units)
Serum protein	10/16: 4.17 Gm., albumin 2.86 Gm., globulin 1.31 Gm., A/G 2.2
Wassermann, Kline and Kahn reactions	10/28: negative
McClure-Aldrich Test	10/18: 6 minutes; 10/25: 13 minutes; 11/8: 38 minutes
	Twin 2
Bone marrow (obtained by aspiration)	10/13: 98,400 nucleated cells per cu. mm., 1.8% myeloblasts, 23.6% neutrophilic myelocytes, 0.4% basophilic myelocytes, 11.2% nonsegmented neutrophils, 4.4% segmented neutrophils, 0.6% eosinophils, 3.8% lymphocytes, 0.6% hematogones, 53.6% nucleated red cells
Platelets	10/11: 150,000; 11/4: 240,000
Urine	10/11 and 10/13: completely normal
Icterus index	10/16: 31.4; 10/26: 19.1
Van den Bergh reaction	10/16: delayed (5.0 units)
Serum protein	10/9: 4.08 Gm., albumin 2.62 Gm., globulin 1.46 Gm., A/G 1.8; 10/16: 2.38 Gm., albumin 1.58 Gm., globulin 0.80 Gm., A/G 2.0
Wassermann, Kline and Kahn reactions	10/28: negative
McClure Aldrich Test	10/25: 6 minutes; 11/18: 46 minutes

Icterus first appeared on the fifth day. It was definite but not marked and did not increase in intensity. Lasting five days, it disappeared on the tenth day. On the eighth day the icterus index was 31.4 and the van den Bergh reaction was delayed (5.0 units).

After the transfusion, the red cell count rose rapidly to over 4,000,000 and the hemoglobin content to over 90 per cent. These levels remained constant for almost four weeks; then gradually increasing anemia developed, which from the age of 5½ weeks to discharge, at 9 weeks, persisted despite treatment, with the red cell count between 2,000,000 and 3,000,000 and the hemoglobin content

culated as follows: 200 : 200 + number of nucleated red cells = absolute number of white cells; total chamber count of nucleated cells.

In the examination of the bone marrow spreads, 500 nucleated cells, including the nucleated red cells, were counted, and the differential count was expressed in percentage.

The reticulocyte percentage was determined by counting 1,000 erythrocytes in a spread stained by a 1 per cent alcoholic solution of brilliant cresyl blue and then by Jenner and Giemsa stains.

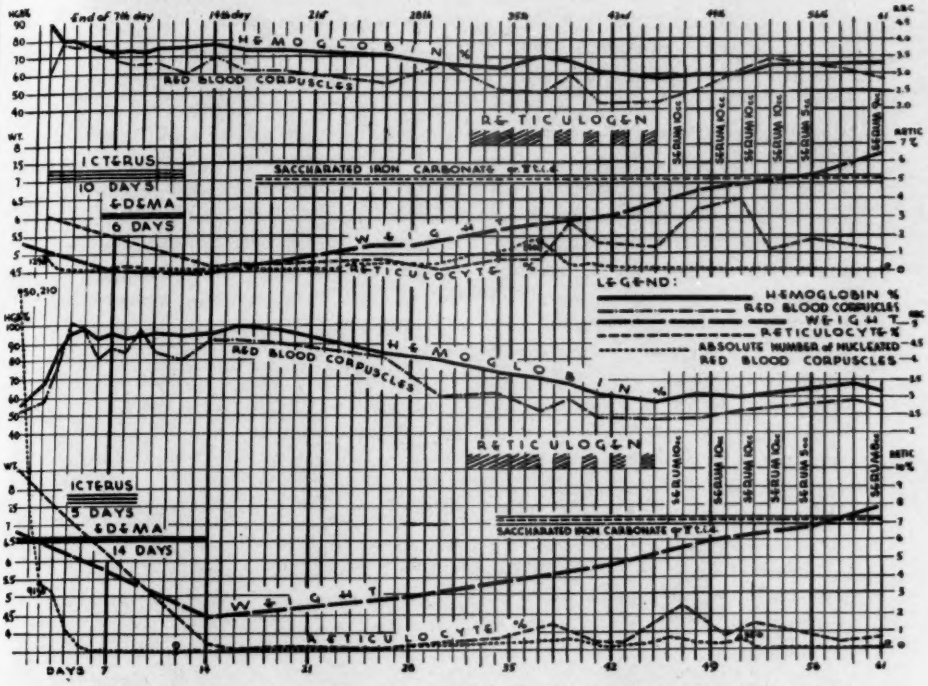


Fig. 2.—Course of the twins during hospitalization (twin 1 upper half, twin 2 lower half).

Fig. 3.—The twins on the eighth day. Twin 2 (on the right) still shows evidence of edema.

between 58 and 68 per cent. Now the picture was that of congenital anemia without erythroblastemia, the nucleated red cells having disappeared from the peripheral circulation during the second week, except for minor aberrations noted in table 2.

There was reticulocytosis (10.1 per cent) on the third day. The value fell to 0.5 per cent at the age of 2 weeks.[23]

Aspiration of sternal bone marrow on the fifth day revealed 53.6 per cent nucleated red cells. This value is definitely above the normal level.[24]

Some reports in the literature have mentioned the effectiveness of parenterally administered liver extract in the treatment of anemia of the newborn.[25] So it was decided to try intramuscular injections of reticulogen, a concentrated liver extract 0.5 cc. of which, according to the manufacturer, is "comparable in hematopoietic effect to . . . 6½-10 lbs. of fresh liver, and also contains 500 International Units of Vitamin B_1." At the age of 4½ weeks, shortly after the levels of red cells and hemoglobin had begun to fall, 0.5 cc. was given every day for five days, then every other day four times, a total of nine injections. In spite of this, the anemia became worse, and there was no rise in reticulocytes.

Administration of 5 grains (0.32 Gm.) of saccharated ferrous carbonate three times a day, begun during the liver therapy and continued until after the patient's discharge, also had no effect.

Two days after the last injection of the liver extract it was decided to determine the effect of human blood serum given intramuscularly. Accordingly, this was administered in doses of approximately 10 cc. at intervals of two to five days, a total of 53 cc. being given over two and a half weeks. Here, too, there was no demonstrable effect.

Discharged at the end of nine weeks, the child weighed 7 pounds and 7½ ounces (3,388 Gm.) and seemed perfectly normal in all respects, except for the anemia (red cells, 2,770,000; hemoglobin, 64 per cent).

Unfortunately, no blood count was made for the normal-appearing twin (1) until he was 2 days of age, at which time the red cell count was 3,080,000 and the hemoglobin content 90 per cent. There were 10,710 white cells, the differential count showing neutrophilic predominance and 2 per cent myelocytes. But there were only 24 nucleated red cells per 200 white cells, or 1,290 per cubic millimeter. The erythrocytes showed anisocytosis, especially macrocytosis, and poikilocytosis.

The significant findings for this twin were as follows (fig. 2):

---

23. Normally, the reticulocyte percentage is 1.4 to 1.9 at birth, with a maximum of 5.5 during the first thirty-six hours. Falling steadily, the value is usually below 0.5 per cent by the tenth day (Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, p. 930).

24. Unpublished data of bone marrow studies in the newborn made by one of us (L. M. S.) indicate that the proportion of nucleated red cells is about one third of all the nucleated cells. A general similarity to the bone marrow picture of older age groups was noted by L. A. Erf and A. Fine (Am. J. M. Sc. **195**:8, 1938) in a case of a premature infant born of a leukemic mother and by K. Kato (Sternal Marrow Puncture in Infants and in Children, Am. J. Dis. Child. **54**: 209 [Aug.] 1937), who examined slightly older infants.

25 (*a*) Gelston, C. F., and Sappington, E. E.: Primary Anemia in the New-Born, Am. J. Dis. Child. **39**:807 (April) 1930. (*b*) Henry, W. A.: Canad. M. A. J. **33**:656, 1935. (*c*) Huenekens, E. J.: J. Pediat. **9**:427, 1936. (*d*) Krost, G. N.: ibid. **10**:613, 1937. (*e*) Schwartz, A. B.: Wisconsin M. J. **33**:98, 1934. (*f*) Abbott and Abbott.[6]

The weight fell gradually from 5 pounds and 5 ounces (2,410 Gm.) to a low point of 4 pounds and 7 ounces (2,013 Gm.) at the thirteenth day, a weight approximately the same as the brother's. Thereafter it increased steadily.

The liver was never palpable.

The spleen was never palpable.

Icterus was first present on the third day of life. It increased to moderate intensity and finally disappeared on the thirteenth day. This jaundice appeared two days earlier, disappeared three days later and was more intense than in the hydropsic infant. On the eighth day the icterus index was 44.0, and the van den Bergh reaction was biphasic (7.5 units). On the eighteenth day the icterus index was 13.7.

Fig. 4.—The twins at 1 month of age. Twin 2 (on the right) now weighs slightly less than his brother.

At the end of the first week, slight edema of the scalp and extremities was noted. It persisted for six days, during which time the McClure-Aldrich [26] test showed a disappearance time of six minutes.[27] A week later this was thirteen

26. McClure, W. B., and Aldrich, C. A.: Time Required for the Disappearance of Intradermally Injected Salt Solution, J. A. M. A. **81**:293 (July 28) 1923.

27. This nonspecific test for edema is performed by the intracutaneous injection of 0.2 cc. of a physiologic solution of sodium chloride, which produces a wheal. The speed with which the wheal disappears is directly related to the amount of edema present.

In testing a series of normal infants in the newborn period, we found the average disappearance time to be slightly over twenty minutes (Shapiro, L. M.: The Intradermal Saline Test [McClure-Aldrich] in the Newborn, J. Pediat., to be published).

minutes, and two weeks after that, at the age of 1 month, it was thirty-eight minutes.

In retrospect, it seems that the excessive loss of weight in this case was in part due to the disappearance of latent edema, for by the thirteenth day the child weighed 14 ounces (397 Gm.) less than at birth.

During the first week the hemoglobin level fell below 80 per cent, and for the first four weeks it hovered between 73 and 77 per cent, while the red cell count was a little over 3,000,000. At the end of four weeks a drop in red cell and hemoglobin values began, corresponding to conditions in twin 2. However, the hemoglobin level of twin 1 was 15 per cent lower and the red cell count 2,000,000 lower than in the case of his brother.

From the age of 5½ weeks to discharge, the red cell counts and hemoglobin levels of the two babies were almost identical, hovering between 2,000,000 and 3,000,000 and 58 and 68 per cent, respectively.

In the case of twin 1, a few nucleated red cells were seen during the first week of life, disappearing almost completely from the circulation after the second week but reappearing in small numbers after four weeks (table 1).

There was a reticulocyte count of 3 per cent on the third day. It fell to 0.2 per cent at the age of 2 weeks.

Aspiration of sternal bone marrow was performed on the fourth day. Unlike the high percentage of nucleated red cells observed in the case of the other child, who also had marked erythroblastemia, the percentage for twin 1 was 34.8 per cent, within normal limits.

Because of the anemia, administration of 5 grains (0.32 Gm.) of saccharated ferrous carbonate three times a day was started in the third week (two weeks before this therapy was begun for twin 2) and continued through discharge, with no effect on the blood picture.

As in the case of the edematous twin, nine injections of liver extract and administration of 54 cc. of human blood serum failed to alter the blood picture to any appreciable extent.

When discharged, at the end of nine weeks, the child weighed 7 pounds and 11 ounces (3,487 Gm.), 3½ ounces (99 Gm.) more than his twin, and seemed likewise perfectly normal in all respects except for the anemia (red cells, 2,830,000; hemoglobin, 66 per cent).

Comparison of Significant Findings

	Twin 1	Twin 2
Edema	Latent	Marked
Icterus	Moderate	Slight
Erythroblastemia	Slight (?)	Marked
Reticulocytosis	Normal	High
Bone marrow	Normal	Hyperplastic
Anemia	Present	Present
Liver	Not palpable	Palpable
Spleen	Not palpable	Not palpable
Serum protein	Low	Low

Since discharge the children have led the lives of perfectly normal infants. They are robust in appearance, happy and alert. Hypochromic anemia (tables 1 and 2) at present is being treated with an iron compound. The cause is most likely a deficiency of iron, so common in twins and among children of poor families.

TREATMENT

Unquestionably an important factor in saving the life of twin 2 was that the blood transfusion was given only six hours after birth, with a strikingly rapid rise in the levels of red blood corpuscles and hemoglobin. We are in accord with the idea that the frequency of transfusion should be guided by the clinical and hematologic picture presented by the patient and not determined arbitrarily.[28] All one should seek to achieve is a maintenance of a red blood cell and a hemoglobin level adequate to maintain life, for if the child survives the first few weeks of life there is a tendency toward self limitation of the disease process and spontaneous recovery, whereas too many transfusions may cause increased hemolysis.

Fig. 5.—The twins at 7 months of age. Twin 2 is on the right.

Large doses of liver extract administered intramuscularly failed to halt the increasing anemia in our twins. The results reported by others have been variable.[28] We feel that the disease is not related to pernicious anemia but agree that further investigation with liver extract should be considered, for Cooley [28] mentioned that better success was obtained with the whole extract rather than with the anti-pernicious-anemia fraction.

The usefulness of intramuscularly administered human blood serum was strongly advocated by Hampson, in 1929,[29] and more recently by Krost, in 1937.[25d] In our cases we noted that although serum caused no striking improvement, at least there was no further fall in the red cell and hemoglobin values. We do not feel that the findings

28. American Academy of Pediatrics: Round Table Discussion on Anemia of the Newborn, J. Pediat. **13**:143, 1938.

29. Hampson, A. C.: Lancet **1**:429, 1929.

just mentioned warrant a definite interpretation, for it must be borne in mind that the serum was given at a time when spontaneous recovery may have been taking place. However, if it can be further established that early administration of serum is a helpful adjuvant measure, it may be worth while for a hospital service to have a supply of serum on hand. This can be given as soon as the diagnosis is made, while the patient is waiting for the transfusion.

EDEMA

The interpretation of the low figures for the serum protein of the twins must also be left for the future. In case of twin 2 the serum protein value [30] on the first day was 4.08 Gm. per hundred cubic centimeters, falling on the eighth day to 2.38 Gm., even though the edema was diminishing. In case of twin 1 it was 4.17 Gm. on the eighth day. Although Darrow and Cary [31] found an average value of 4.94 Gm. for 26 premature infants, there may be a temptation here to ascribe the low serum protein level to damage of the liver, which is known to occur in this disease. Since there was no albuminuria, it is fair to assume that the low figures were due to defective formation and not to increased loss of protein.

As twin 2 was not suffering from anoxemia clinically or hematologically (hemoglobin level not less than 56 per cent) and as the edema was improving while the serum protein value fell, it seems to us that the true cause of the edema may best be explained on the basis of generalized capillary permeability. There is no doubt that marked anemia and erythroblastemia are important contributing factors.

CASES REPORTED IN THE LITERATURE

The presence of universal edema and of anemia of the newborn in our twins led us to investigate the incidence in twins of the various manifestations of the triad. In all, we found 16 reports, which are summarized in chronologic order:

1.—About 1605 Bourgeois [32] reported on premature monochorionic twin girls, one of whom had hydrops, the other being normal.

2. In 1873 Church [33] mentioned full term twins, both of whom died with icterus gravis. The sex was not given. In a family of numerous jaundiced infants they were the thirteenth and fourteenth of seventeen children, only two of whom lived beyond the ninth day.

---

30. Kjeldahl method with nesslerization.

31. Darrow, D. C., and Cary, M. K.: J. Pediat. **3**:573, 1933.

32. Bourgeois, L., cited by Ballantyne, J. W.: The Diseases and Deformities of the Foetus: An Attempt Towards a System of Ante-Natal Pathology, Edinburgh, Oliver & Boyd, 1892-1895.

33. Church, A. S.: New York M. J. **18**:199, 1873.

3.—In 1888 Tarnier and Budin [34] mentioned dichorionic twins, one of whom had hydrops, the other being normal. Only the membranes of the edematous twin were infiltrated. The sex was not given.

4.—In 1901 Andrews [35] described premature twins, the first being an apparently normal girl who died after four hours. The edematous boy died immediately after birth. The microscopic picture of the liver was significant.

5.—In 1907 Bleneke [36] reported on twins with kernicterus. The familial history was significant. Autopsy was performed on only one twin, a boy. The sex of the other was not mentioned.

6.—In 1916 Wooley [37] mentioned premature twins, one apparently normal and the other anasarcous. The sex was not given.

7.—In 1919 Prins [38] described a family with gravely jaundiced siblings, in which icteric twins died on the third day. The sex was not mentioned.

8.—In 1922 Capon [39] wrote of binovular stillborn premature twin girls. The first was edematous, and the second was normal. Necropsies revealed no anatomic anomalies.

9. In 1925 Taylor [40] described twin girls, one of whom died at 3 days and the other at 7 days. Both had jaundice and convulsions. The familial history gave evidence of the disease.

10.—In 1927 Oberndorfer [41] reported on uniplacental premature twins of a family having a long succession of children who were edematous at birth. Both died. One was normal, and the other was proved to have universal edema of the Schridde type. The sex was not mentioned.

11.—In 1928 Huwer [42] described postmature twins, a girl and a boy, both of whom were jaundiced three hours after birth and died with cyanosis and convulsions within forty-eight hours. Kernicterus was observed in both at autopsy.

12.—In 1928 Foote [43] reported a case of congenital anemia in a premature girl, who survived after transfusions. The twin brother was normal.

13.—In 1929 Hampson [29] referred to twins he had seen, one of whom had icterus gravis, the other being normal. The sex was not mentioned.

14. In 1930 Jewesbury [44] mentioned premature twins with icterus gravis, both of whom died. The sex was not given. The familial history gave evidence of the disease.

15.—In 1932 de Lange [12g] described twins, both of whom died shortly after birth. The boy, the first born, had icterus gravis, and the girl had hydrops. The familial history gave evidence of the disease.

---

34. Tarnier, S., and Budin, P.: Traité de l'art des accouchements, Paris, G. Steinheil, 1888, vol. 2, p. 352.
35. Andrews, H. R.: Tr. Obst. Soc. London **43**:166, 1901.
36. Bleneke, R.: München. med. Wchnschr. **54**:2023, 1907.
37. Wooley, P. G.: J. Lab. & Clin. Med. **1**:347, 1916.
38. Prins, G. A.: Nederl. tijdschr. v. geneesk. **2**:1880, 1919; abstracted, J. A. M. A. **74**:838 (March 20) 1920.
39. Capon, N. B.: J. Obst. & Gynaec. Brit. Emp. **29**:239, 1922.
40. Taylor, W. M.: Brit. M. J. **1**:1127, 1925.
41. Oberndorfer, S.: Zentralbl. f. Gynäk. **51**:1830, 1927.
42. Huwer, G.: Ztschr. f. Geburtsh. u. Gynäk. **94**:150, 1928.
43. Foote, J.: Arch. am. de med. **4**:39, 1928.
44. Jewesbury, R. C.: Proc. Roy. Soc. Med. **23**:1112, 1930.

16.—In 1937 Bushnell and Aldrich [45] reported the case of a girl, the first born of fraternal twins in a family with a questionably significant history. The infant apparently had icterus gravis, which responded to treatment with transfusions. She died suddenly at 13 months. The sex of the other child was not mentioned.

COMMENT

Most of the reports cited are brief and incomplete, but with the possible exception of the first [32] they all appear to deal with the disease in question. On the other hand, in Ballantyne's [46] 19 collected cases of hydrops occurring in one of twins, all but 2 cases presented some anatomic anomaly to account for the edema.

Seven of the reports deal with fraternal twins, but only 3 of the remaining 9 reports suggest that the twins may have been identical.

TABLE 4.—*Anthropometric Measurements at the Age of Thirteen Months* *

	Twin 1	Twin 2		Twin 1	Twin 2
Cephalic length	169	168	Head, circumference	473	479
Cephalic breadth	135	132	Chest, circumference	446	446
Facial diameter	98	98	Humerus, length	133	130
Bizygomatic diameter	97	101	Radius, length	99	102
Bigonial diameter	73	72	Hand, length	89	89
Nasal prosthion	42	42	Palm, length	51	52
Infradental mentum	26	27	Palm, breadth	44	43
Nasal height	32	32	Finger, length	47	46
Nasal breadth	27	27	Femur, length	197	193
Palpebral length	25	26	Tibia, length	128	128
Inter-inner canthi	27	26	Tibia-sole	165	167
Ear, length	52	54	Foot, length	113	114
Ear, breadth	37	36	Foot, breadth	48	45
Biacromial diameter	182	184	Sitting height	489	484
Bi-iliac diameter	127	127	Vertex	764	741

* All measurements are expressed in millimeters. Unilateral measurements were made on the right.

We believe that our twin boys, born with a single placenta, are identical for the following reasons:

1. Their general appearance pointed to this fact (fig. 5).

2. Prints of the soles and palms, taken at the age of 13 months, and examined by Dr. F. Schiff, showed minimal differences in the two children.

3. Thirty anthropometric measurements [47] taken at 13 months revealed a close similarity (table 4).

45. Bushnell, L. F., and Aldrich, C. A.: Erythroblastosis Foetalis: Report of a Case in Which There Were Clinical Signs of Kernicterus Without Postmortem Confirmation, Am. J. Dis. Child. **53**:1053 (April) 1937.

46. Ballantyne, J. W.: The Diseases and Deformities of the Foetus: An Attempt Towards a System of Ante-Natal Pathology, Edinburgh, Oliver & Boyd, 1892-1895.

47. These measurements were taken through the courtesy of Dr. H. Bakwin.

4. When the children were 6 months old, serologic examinations were done by Dr. Schiff as to the blood groups and the factors M and N. Both children were found to have blood of group A as well as the combination MN. This is significant, for when both these tests are applied identical twins will show the same picture in 100 per cent of the cases, whereas fraternal twins will show the same picture in only 25 per cent.[48] As a further step, the subtype of the blood group was investigated, and both children proved to have subtype 1. Serologically, the blood of both twins may be described as A-1MN.

Table 5 gives the possible combinations of conditions.

TABLE 5.—*Combinations of Diseases of Twins Reported in the Literature*

Combination	No. of Cases	Authors Reporting on Identical Twins	Authors Reporting on Twins with Questionable Relationship	Authors Reporting on Fraternal Twins
Hydrops and hydrops	0	.....	.....	.....
Hydrops and icterus gravis	1	.....	.....	de Lange (1932)
Hydrops and anemia	1	Shapiro and Cohen	.....	.....
Hydrops and normal status	6	Bourgeois (?) (1605) Oberndorfer (?) (1927)	Wooley (1916)	Tarnier and Budin (1888) Andrews (1901) Capon (1922)
Icterus gravis and icterus gravis	6	Taylor (?) (1925)	Church (1873) Bleneke (1907) Prins (1919) Jewesbury (1930)	Huwer (1928)
Icterus gravis and anemia	0	.....	.....	.....
Icterus gravis and normal status	2	.....	Hampson (1929)	Bushnell and Aldrich (1937)
Anemia and anemia	0	.....	.....	.....
Anemia and normal status	1	.....	.....	Foote (1928)

The fact that in the general population the incidence of fraternal twins is greater than that of identical twins suggests that in most of the cases "questionable" probably indicates fraternal twins.

Although little has been published on the hereditary factor,[49] it is widely believed that heredity plays an important part in this diversified process. The paucity of significant data concerning twins with the disease is unfortunate, for careful studies of twins presenting any of the various manifestations of this entity will contribute to a better understanding of its etiology.

48. Schiff, F., and von Verschuer, O.: Ztschr. f. Morphol. u. Anthropol. **32**: 244, 1933.

49. Macklin, M. T.: Erythroblastosis Foetalis: Study of Its Mode of Inheritance, Am. J. Dis. Child. **53**:1245 (May) 1937.

SUMMARY

We believe that these twins were proved to be identical.

In congenital hydrops and anemia of the newborn they presented different clinical manifestations of what we consider to be the same disease.

Despite different onsets, the 2 patients after the age of 5½ weeks presented the same clinical and hematologic picture.

The level of serum protein was low in both cases, with no inversion of the albumin-globulin ratio.

The bone marrow was hyperplastic in the edematous infant but not in his brother.

The intradermal saline test (McClure-Aldrich) was of value in following the disappearance of latent edema.

Various forms of therapy were used: (*a*) An iron compound was ineffective. (*b*) A concentrated liver extract (Reticulogen) was ineffective. (*c*) Human blood serum caused no appreciable change in the anemia. The interpretation of this is open to question. (*d*) Blood transfusion is the most effective agent, especially when given early and, if necessary, frequently.

Twin 2 is the only patient reported to have hydrops who recovered.

These twins may be important from the standpoint of suggesting the hereditary factor in this disease.

CONCLUSIONS

We believe that universal edema of the newborn, icterus gravis and anemia of the newborn are different clinical manifestations, probably due to quantitative changes, of the same underlying disease process. Moreover, since members of this disease group may or may not be associated with evidence of erythroblastosis or erythroblastemia,[50] the proper terminology is still a matter for the future to decide.

1 West Seventy-Fourth Street

1175 Park Avenue

50. Brown, S. S.; Morrison, M., and Meyer, D. A.: Anemia of the New-Born Without Erythroblastosis: Observations at Autopsy, Am. J. Dis. Child. **48**:335 (Aug.) 1934. Cohen, P.: J. Pediat. **7**:220, 1935. Pasachoff and Wilson (footnotes 3 and 19).

SPORADIC CONGENITAL GOITER CAUSING DEATH OF AN INFANT

LEON SOLIS-COHEN, M.D.
AND
MEYER STEINBACH, M.D.
PHILADELPHIA

Although thyroid enlargement in the newborn is not uncommon in certain districts where goiter is endemic, a perusal of the literature reveals surprisingly few instances of sporadic congenital goiter.

McCarrison found goiter in nursing infants in the regions of India where goiter is endemic. In some Himalayan villages 60 per cent of infants at the breast have goiter. According to Wieland, congenital goiter is common in Switzerland. About 50 per cent of untreated mothers gave birth to goitrous children in the Canton of Appenzall. Skinner reported an unusually high incidence of congenital goiter in the state of Washington. He found that 10 per cent of untreated mothers had goitrous babies. On the other hand, congenital goiter is practically unheard of in the Great Lakes goiter belt. In Ohio and Minnesota, where there has been a high incidence of simple goiter (particularly before the period of iodine prophylaxis), the incidence of cretinism is low, and congenital goiter has not been reported. Means, in his comprehensive book on thyroid disease, failed to mention congenital goiter. Nor does one find any record of this condition in the reports of the Mayo or the Crile Clinic. Bram reported that in 16,000 cases of goiter he had not observed a single case in which the disease occurred in a newborn infant. White, Sweet, Neurath, Căprioară and others have reported sporadic cases. Hill briefly reviewed the subject up to date and added his own case, which parallels ours in some respects.

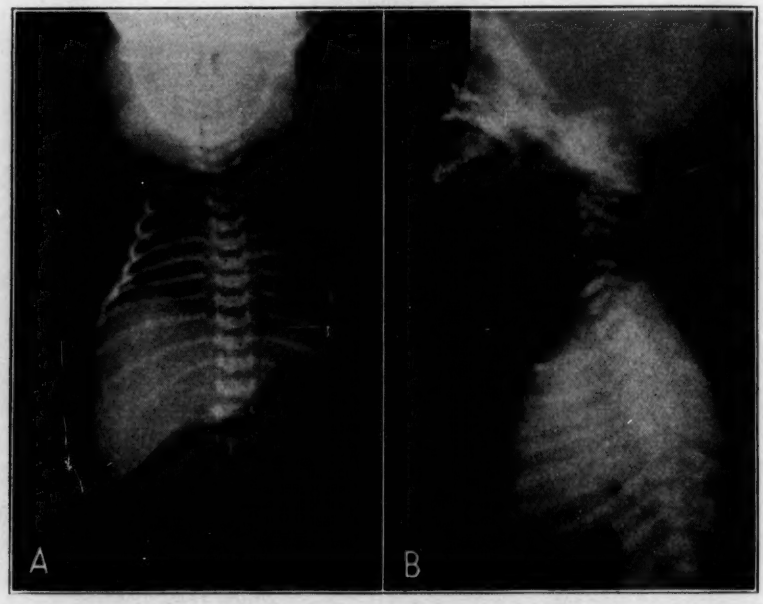
REPORT OF A CASE

Clinical History.—D. G. was born spontaneously, weighing 7 pounds and 10 ounces (3,459 Gm.). The infant had short legs and a long body; six toes were present on each foot and six fingers on the right hand. There were cyanosis and considerable dyspnea. The child refused to nurse. A large bilateral swelling on both sides of the neck was observed. It was moderately firm to the touch. The Wassermann reaction of the cord blood was 4 plus. The baby became progressively more dyspneic and died in less than forty-eight hours, apparently of pressure asphyxia.

From the Department of Radiology, Memorial Hospital.

Family History.—While the mother of the infant presented no visible goiter, her myxedematous appearance and low intelligence level suggested a hypothyroid constitution. She had previously had two miscarriages, and there were two living children. Inquiry further revealed that Mrs. G.'s mother had had a goiter removed. The Wassermann reaction of Mrs. G.'s blood was strongly positive. Unfortunately, before further studies could be made, she moved away to escape antisyphilitic treatment.

Postmortem Examination.—Roentgen Observations: In the region of the thyroid, protruding anteriorly and laterally, there was a large, evenly outlined mass which appeared to represent a congenital goiter. The supracardiac shadow was widened, owing to enlargement of the thymus gland.



Postmortem roentgenograms of the patient. In *A*, note the broadened mediastinal shadow at the base of the heart, indicative of enlargement of the thymus gland, and the shadow of soft tissue in the neck. In *B*, observe the shadow of the enlarged thyroid gland and displacement of the airway. Note also compression stenosis of the trachea due to posterior enlargement of the thymus gland.

Gross Observations: There was a large bilobar goiter, the two lobes being connected by an enlarged isthmus. The thyroid gland weighed 41 Gm. It encircled both the trachea and the esophagus, causing pressure constriction of each. The lungs were partially collapsed. The heart was normal in size, shape and position. The thymus gland showed bilobar enlargement, covering the heart anteriorly and laterally. It weighed 10 Gm.

Microscopic Observations: There was hyperplasia of acini. Colloid was absent. The thymus gland showed simple hypertrophy.

COMMENT

While the Wassermann reaction of the umbilical cord blood was positive, microscopic section failed to reveal any evidence of congenital syphilis. Of course, manifestation of congenital syphilis only in later life is entirely possible. However, there does not appear to be any ground for suspecting a relationship between the goiter and syphilis. Standard works on syphilis make no mention of goiter in association with congenital syphilis. Neither Jeans and Cooke nor Stokes even mentioned thyroid enlargement. The thyroid in a newborn infant may occasionally be the seat of a syphilitic process, but it apparently never undergoes goitrous change as a result of syphilis.

Furthermore, although the existence of anomalies (supernumerary digits) raises interesting speculation, we believe that in this case it was purely coincidental.

Etiology.—Knowledge of the cause of endemic goiter is still incomplete. The role of iodine deficiency has been well established, especially in the principal goiter belts (Marine and Kimball). Skinner prevented congenital goiter by feeding the mothers iodine. In addition, McCarrison showed that contaminated water in the goiter districts of India also plays an important part in the causation of goiter. Other factors, such as vitamin deficiency and unbalanced mineral ratios in the diet, may be also responsible, but the determination of their exact significance awaits future work. Wieland pointed out that congenital goiter occurs only in areas where goiter is severely endemic and that the incidence is roughly proportional to the prevalence of the condition. The same rule obtains for the incidence of cretinism. While cretins in areas where cretinism is endemic may or may not have goiter, the sporadic variety of cretinism is rarely characterized by thyroid enlargement. Simple goiter, myxedema, congenital goiter and cretinism simply represent different grades of hypothyroidism or athyroidism. A pregnant woman herself suffering from insufficient thyroid metabolism surely lacks enough thyroid hormone for her developing fetus. According to the degree of insufficiency, the fetal thyroid either undergoes hypertrophy to compensate for the lack of hormone or, with the more severe deficiency, suffers complete destruction of its secretory function.

Pathology.—Normally the thyroid gland in a newborn infant in nongoitrous districts weighs no more than 1 or 2 Gm. According to Wegelin, thyroids of normal infants in goiter belts weigh 5 to 10 Gm. Rarely does an enlarged thyroid exceed 30 Gm. in weight. However, in Hill's case and in our own the thyroid weighed well over 30 Gm. Microscopically, congenital goiter may show parenchymatous, colloid, fibrous or nodular changes, with the first type predominating.

Symptomatology.—Aside from the specific physiologic and morphologic manifestations of thyroid insufficiency, the acute symptoms in these cases depend on the size of the goiter and its mechanical effect on respiration. The child may suffer from only slight tracheal pressure, and adequate treatment may produce sufficient improvement to permit of further development. However, when the condition is extreme, as in our case, the enlarged thyroid causes pressure asphyxia. In our case the baby lived less than forty-eight hours, and in Hill's case the child lived almost four days. In most of Skinner's cases the babies lived. In Sweet's cases the patient recovered with iodine therapy. The dyspneic child nurses unsatisfactorily if at all, this factor also contributing to the fatal outcome.

Prognosis.—If a child survives the first week, chances for its recovery are fairly good.

Treatment.—When a goiter constitutes an emergency and threatens the life of the infant, it seems reasonable to perform a tracheotomy while attempts are made to reduce the size of the thyroid. However successful such efforts may prove, the rational approach obviously lies in the direction of prophylaxis. Adequate treatment of the mother will almost invariably prevent congenital goiter.

SUMMARY

A rare case of sporadic congenital goiter causing death of an infant is presented.

The associated syphilis of the mother and the positive Wassermann reaction of the cord blood, together with the anomalous extra digits, are regarded as coincidental phenomena unrelated to the thyroid enlargement.

Congenital goiter is common in areas where goiter is severe and endemic, such as certain parts of Switzerland, the Himalayas of India and the state of Washington.

The thyroid in our case is one of the largest on record.

An extremely enlarged thyroid may cause asphyxia and death.

Rational therapy is directed to the elimination of thyroid deficiency in the mother. The possibility that tracheotomy may save life is suggested.

BIBLIOGRAPHY

Brame, I.: Arch. Pediat. **54**:419-424 (July) 1937.

Căprioară: Cluj. med. **15**:206-212 (April) 1934.

Giudici, E.: Ann. di ostet. e ginec. **59**:323-347 (March 31) 1937.

Griebe, H. G.: Canad. M. A. J. **15**:187-188 (Feb.) 1925.

Griffith, J. P. C., and Mitchell, A. G.: The Diseases of Infants and Children, ed. 2, Philadelphia, W. B. Saunders Company, 1937.

Hill, A. L.: Arch. Pediat. **50**:424-430 (June) 1933.

Jeans, P. C., and Cooke, J. V.: Prepubescent Syphilis, New York, D. Appleton and Company, 1930.

Joll, C. A.: Diseases of the Thyroid Gland, with Special Reference to Thyrotoxicosis, St. Louis, C. V. Mosby Company, 1932.

McCarrison, R.: Brit. M. J. **1**:24-31 (Jan. 2) 1937; Thyroid Gland in Health and Disease, London, Baillière, Tindall & Cox, 1917, p. 88; Recent Researches in the Etiology of Goitre, in Report of the International Conference on Goiter, Berne, 1933.

Means, J. H.: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937.

Neumann, H. O.: Arch. f. Gynäk. **163**:368-405, 1937.

Neurath, R.: Wien. klin. Wchnschr. **38**:1206-1207 (Nov. 5) 1925.

Sheldon, W.: Diseases of Infancy and Childhood, Philadelphia, P. Blakiston's Son & Co., 1936.

Skinner, H. H.: M. J. & Rec. **127**:381-383 (April 4) 1928.

Stokes, J. H.: Modern Clinical Syphilology, ed. 2, Philadelphia, W. B. Saunders Company, 1934.

Sweet, P. W.: Northwest Med. **27**:183-184 (April) 1928.

White, C.: J. Obst. & Gynaec. Brit. Emp. **21**:231-233, 1912.

Wieland, E.: Schweiz. med. Wchnschr. **57**:850-852 (Aug. 27) 1927.

Progress in Pediatrics

ROLE OF ACID-SOLUBLE PHOSPHORUS COMPOUNDS IN RED BLOOD CELLS

IN EXPERIMENTAL RICKETS, RENAL INSUFFICIENCY, PYLORIC OBSTRUCTION, GASTROENTERITIS, AMMONIUM CHLORIDE ACIDOSIS AND DIABETIC ACIDOSIS

GEORGE M. GUEST, M.D.
AND
S. RAPOPORT, M.D.
CINCINNATI

This discussion of the acid-soluble phosphorus compounds of the red blood cells concerns chiefly their importance in the acid-base equilibrium of the blood and their probable role in the intermediate phosphorus metabolism of the body. It is based on clinical and experimental studies of a variety of conditions in which large changes in the concentration of acid-soluble phosphorus in the blood cells are found. Examples from these studies are presented to demonstrate the changes which have been found associated with rickets, bilateral nephrectomy, alkalosis of pyloric obstruction and different types of acidosis. As a basis for the interpretation of the findings in these conditions, current concepts of the glycolytic cycle in blood are summarized briefly, since the reactions of the glycolytic process are responsible for the synthesis and hydrolysis of the organic phosphorus compounds with which these studies are concerned.

METHODS

Values for inorganic and organic acid-soluble phosphorus were determined by the method of Fiske and Subbarow,[1] with minor modifications.[2] The value for

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati.

Presented by S. Rapoport to the Department of Biochemistry of the Graduate School, University of Cincinnati, in part fulfilment of the requirements for the degree Ph.D.

Presented at Toronto, April 27, 1939, by G. M. Guest as part of a symposium of the American Society of Biological Chemists and the American Physiological Society on the Chemistry and Physiology of the Red Blood Cells.

1. Fiske, C. H., and Subbarow, Y.: Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

2. Guest, G. M., and Rapoport, S.: Effects of Overdosage of Irradiated Ergosterol in Rabbits: Changes of Diphosphoglyceric Acid in the Blood Cells, J. Biol. Chem. **124**:599, 1938.

adenosinetriphosphate was determined by the method of Lohmann,[3] the "pyrophosphate" fraction obtained by seven minutes' hydrolysis with boiling normal sulfuric acid being multiplied by 1.5 to give the value designated as "adenosinetriphosphate."[4] The value for diphosphoglycerate was determined by the method of Rapoport.[5] Values for chlorides were determined either by the method of Van Slyke and Sendroy[6] or by the method of Sendroy.[7] The value for carbon dioxide was determined by the method of Van Slyke and Neill, with use of the factors of Van Slyke and Sendroy.[8] The value for total base (total inorganic cations) was determined by the method of Leva and Guest.[9] The p_H was determined with the glass electrode. The percentage volume of cells in heparinized blood was determined by the method of Guest and Siler,[10] and the concentrations of cellular constituents were calculated indirectly, by means of the cell volume, from values determined for whole blood and serum.

DISTRIBUTION OF ACID-SOLUBLE PHOSPHORUS FRACTIONS IN NORMAL HUMAN RED BLOOD CELLS

The following values represent the usual ranges of concentrations of the inorganic phosphorus and four fractions of the organic acid-soluble phosphorus found in normal human red blood cells:

The inorganic phosphorus concentration usually ranges between 1 and 3 mg. per hundred cubic centimeters. The values tend to be higher in infants and young animals than in older subjects.

The organic acid-soluble phosphorus concentration is usually between 50 and 60 mg. per hundred cubic centimeters, most often nearer 50 mg.

The adenosinetriphosphate phosphorus concentration is usually between 9 and 12 mg. per hundred cubic centimeters, the average being near 10 mg.

Estimates of hexosephosphates must be based on indirect evidence, since these compounds have not yet been isolated in pure form from blood. Available data indicate, however, that both the monophosphate

3. Lohmann, K.: Ueber das Vorkommen und den Umsatz von Pyrophosphat in Zellen: Nachweis und Isolierung des Pyrophosphats, Biochem. Ztschr. **202**: 466, 1928.

4. Rapoport, S., and Guest, G. M.: The Decomposition of Diphosphoglycerate in Acidified Blood: Its Relationship to Reactions of the Glycolytic Cycle, J. Biol. Chem. **129**:781, 1939.

5. Rapoport, S.: Ueber die Bestimmung der Glycerinsäure in freier und veresterter Form, Biochem. Ztschr. **289**:406, 1937.

6. Van Slyke, D. D.: Determination of Chlorides in Blood and Tissues, J. Biol. Chem. **58**:523, 1923.

7. Sendroy, J., Jr.: Microdetermination of Chloride in Biological Fluids, with Solid Silver Iodate: II. Titrimetric Analysis, J. Biol. Chem. **120**:405, 1937.

8. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 2, p. 283.

9. Leva, E., and Guest, G. M.: A Method for the Determination of Total Base (Sum of Sodium, Potassium, Calcium and Magnesium) in Blood, J. Biol. Chem. **130**:777, 1939.

10. Guest, G. M., and Siler, V. E.: Centrifuge Method for Determination of Volume of Cells in Blood, J. Lab. & Clin. Med. **19**:757, 1934.

and the diphosphate esters are present in the blood cells and that these together normally account for approximately 15 mg. of phosphorus per hundred cubic centimeters of cells.

Diphosphoglycerate normally makes up about half of the organic acid-soluble phosphorus, i. e., from 25 to 30 mg. per hundred cubic centimeters.

These figures are nearly the same for the cells of dogs but are higher for the cells of rabbits and rats, the other species used in the experimental studies which are cited here.

THE GLYCOLYTIC CYCLE[10a] IN BLOOD

The synthesis and hydrolysis of organic acid-soluble phosphorus compounds in the red blood cells are accomplished by reactions which form part of the glycolytic cycle in blood. In this, the glycolytic process has an important biologic function apart from the breakdown of sugar:

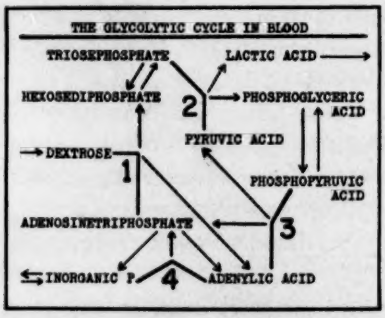


Chart 1.—The glycolytic cycle in blood: a diagram based on current theories of Meyerhof, Parnas, Dische and others.

namely, the regulation of the concentration at which these phosphorus compounds are carried in the blood under different conditions.

The schematic representation of the glycolytic cycle in blood shown in chart 1 is based on theories of Embden, Meyerhof, Parnas, Dische and others. The diagram is designed to illustrate the principal steps in blood glycolysis as they may be described according to current concepts and to show some of the interrelations that can be traced between the phosphorus compounds subsequently discussed.

Dextrose is represented going into, and lactic acid out of, the cycle, while inorganic phosphorus may go in either direction. A reaction, *1*, between dextrose and adenosinetriphosphate yields hexosediphosphate and adenylic acid. Hexosediphosphate is maintained in enzymatic

10a. In chart 1 and in the discussion of the glycolytic cycle, the authors' term "glucose" has been changed to "dextrose" to conform with the style of the American Medical Association Press, based on the terminology of the Pharmacopeia of the United States.

equilibrium with 2 mols of triosephosphate. Reactions, *2*, between triosephosphate and pyruvic acid lead to the formation of phosphoglyceric acid and lactic acid. Phosphoglyceric acid is converted to phosphopyruvic acid, and this in turn reacts with adenylic acid in the resynthesis, *3*, of adenosinetriphosphate, thus completing the cycle. The pyruvic acid liberated in this reaction reacts anew with triosephosphate in the synthesis, *2*, of phosphoglyceric acid. Adenosinetriphosphate is also formed by direct phosphorylation, *4*, of adenylic acid from inorganic phosphate. This esterification, *4*, of inorganic phosphorus is closely linked with the reactions, *2*, between pyruvic acid and triosephosphate.

It is important to note here that all changes of organic acid-soluble phosphorus which are to be discussed hinge on the last-named set of reactions. The synthesis of adenosinetriphosphate by direct phosphorylation of adenylic acid seems to be the only way in which phosphorus can enter this cycle and the only means by which the concentrations of the organic acid-soluble phosphorus compounds can be increased. The hydrolysis of adenosinetriphosphate seems to be at least the most important route by which the phosphorus compounds can be reduced and phosphorus can leave the cycle.

The concentrations of organic acid-soluble phosphorus in the blood cells thus are necessarily subject to the influence of various factors affecting the glycolytic system. One important factor is the p_H of the blood. In experiments with blood in vitro, it has been shown [4] that even slight shifts in the p_H of the blood from a normal level toward greater acidity or alkalinity, respectively, favor the decomposition or the synthesis of diphosphoglycerate in the cells. This effect is seen in various types of acidosis, in which the concentration of diphosphoglycerate in the blood cells is reduced, and in alkalosis, in which the diphosphoglycerate content is increased. Another important factor influencing the concentration of acid-soluble phosphorus in the cells appears to be the supply of phosphorus available. In nephritis and other conditions with impairment or suppression of renal function, the inability to excrete waste endogenous phosphates leads to the accumulation of an excess of inorganic phosphates in the blood; with this the concentration of diphosphoglycerate in the cells is greatly increased. In rickets, on the other hand, with lack of phosphorus low concentrations of organic acid-soluble phosphorus in the cells accompany the well known decreases of inorganic phosphorus in both serum and cells. Examples of these conditions are presented in the following pages.

RICKETS

Chart 2 illustrates changes in the concentrations of different fractions of the acid-soluble phosphorus in the blood cells of rats found during the development of rickets induced by a high calcium, low phosphorus diet and during the healing of rickets induced by a single small dose

of vitamin D. The data on which this chart is based were derived from approximately 260 rats which were used in previously reported experiments.[11]

The values indicated by the starting points of the curves are averages of those found for normal 50 Gm. rats. The dotted lines represent average values found in specimens of the blood of normal rats fed a normal diet, during the age period covered by the rickets experiments. Note that during the first few days of this age period the values for inorganic phosphorus and adenosinetriphosphate phosphorus increase and that the values for organic acid-soluble phosphorus and diphosphoglycerate phosphorus decrease slowly, the latter values reaching constant levels after about twenty-five days.

The solid lines in the left half of chart 2 represent averages of values found during the development of rickets, over a period of twenty-

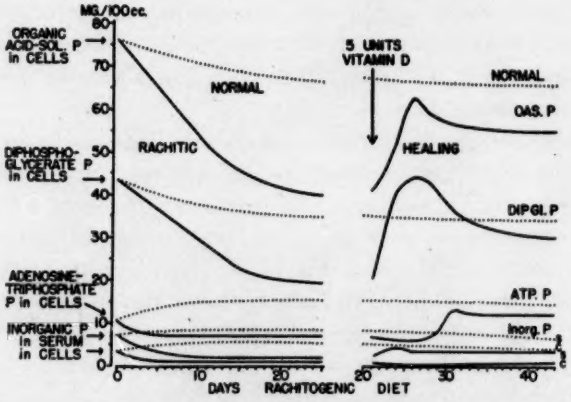


Chart 2.—Changes of acid-soluble phosphorus in the blood of rats during the development and healing of rickets (continuous lines) and in the blood of normal rats (dotted lines) during the same age period.

five days. The solid lines in the right half of the chart represent averages of values found in rats continuously fed the same rachitogenic diet but given a single dose of 5 U. S. P. units of vitamin D on the twenty-first day of the dietary period. The preparation used was drisdol, crystalline vitamin D in propylene glycol, diluted with water.

Development.—The development of rickets in these rats was associated with decreases in all fractions of the acid-soluble phosphorus. During the first five days the concentrations of inorganic phosphorus

11. Rapoport, S., and Guest, G. M.: Changes of Organic Acid-Soluble Phosphorus, Diphosphoglycerate, Adenosinetriphosphate, and Inorganic Phosphorus in the Blood Cells of Rats During the Development and Healing of Rickets, J. Biol. Chem. **126**:749, 1938.

and adenosinetriphosphate phosphorus dropped abruptly to low levels and then remained constant for twenty-five days and longer. The organic acid-soluble phosphorus decreased progressively for about twenty days but thereafter remained constant. The decrease in the organic acid-soluble phosphorus was accounted for almost entirely, after the first few days, in the diphosphoglycerate fraction, which fell to about half its original concentration.

Healing.—The single dose of of 5 U. S. P. units of vitamin D, given on the twenty-first day of the rachitogenic diet, was just sufficient to induce ++++ healing in the epiphyses, as shown by line tests, but this dose was insufficient to restore the rachitic condition completely to normal. After this single dose of vitamin D, the first and the most striking change was the sharp increase in the concentration of diphosphoglycerate phosphorus and of the organic acid-soluble phosphorus in the cells. The diphosphoglycerate phosphorus increased to a concentration considerably above the expected normal level and then, about seven days after the vitamin D was given, decreased again to a point slightly below that level. The adenosinetriphosphate remained practically unchanged for about seven days and then increased, its increase coinciding with the secondary decrease of the diphosphoglycerate. During the first few days after the vitamin D was given, the inorganic phosphorus in the serum rose to about half its normal concentration, but it fell again after five or six days. With this brief increase of the inorganic phosphorus in the serum, the concentration of inorganic phosphorus in the cells fell to 0, rising again only after about seven days. All values were far below normal twenty-two days after the vitamin D was administered.

The time relationships of these changes must be considered to be only approximate because of the variability found among different groups of animals. The sequence of the changes, however, deserves emphasis. During the development of rickets the inorganic phosphorus and the adenosinetriphosphate phosphorus fell quickly to low concentrations, while the concentration of diphosphoglycerate decreased slowly over a longer period; with initiation of healing, the diphosphoglycerate increased first and the adenosinetriphosphate and inorganic phosphorus in the cells later. Recalling the reactions of the glycolytic cycle, one can explain the low concentrations of inorganic phosphorus and adenosinetriphosphate in the cells found immediately after the administration of vitamin D as probably due to the synthesis of phosphoglycerate, which proceeded faster than inorganic phosphorus was supplied to the system.

NEPHRECTOMY

In chart 3 are represented chemical changes found in the blood of a dog during seven days following the removal of both kidneys. The

changes illustrated here are typical of those which we have found, varying in magnitude and accompanying varying degrees of impairment or suppression of renal function, in different clinical and experimental conditions.

After the nephrectomy in this dog, the nonprotein nitrogen in the blood increased at a steady rate, the increase through the seven days being represented by a practically straight line. The increase of inorganic phosphorus was almost as regular as that of the nonprotein nitrogen. The concentration of organic acid-soluble phosphorus in the cells increased from 50 to 97 mg. per hundred cubic centimeters. This

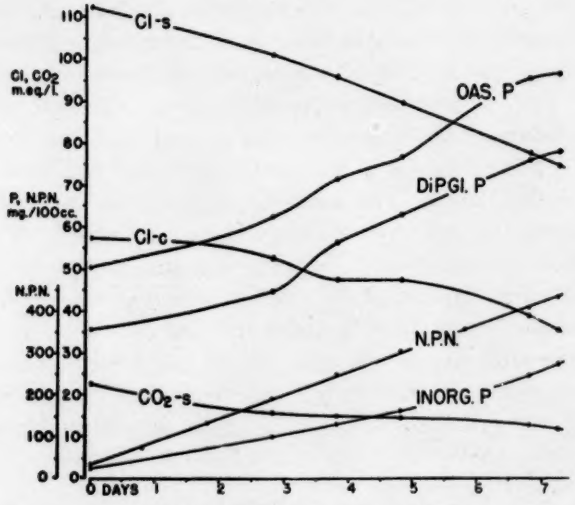


Chart 3.—Changes in the blood of a dog following the removal of both kidneys. (For explanation of abbreviations see chart 2.)

corresponds to findings reported by Ashley and Guest.[12] Here, this increase is closely accounted for at each stage by changes in concentration of the diphosphoglycerate phosphorus which increased from 35 to 78 mg. per hundred cubic centimeters, the increases in organic acid-soluble phosphorus and in diphosphoglycerate phosphorus being, respectively, 47 and 43 mg. per hundred cubic centimeters. It seems reasonable to believe that the increase of organic phosphorus in the cells under such conditions is influenced mainly by the excess of inorganic phosphates accumulating in the blood due to the failure of excretion of the waste endogenous phosphates.

12. Ashley, A., and Guest, G. M.: Distribution of Blood Phosphorus After Suppression of Renal Function, J. Clin. Investigation **13**:219, 1934.

During the seven day period following the nephrectomy, the concentration of chloride in both serum and cells decreased markedly. Here we see a reciprocal relation between changes in the concentrations of diphosphoglycerate and of chloride in the cells, which may be seen again in other conditions as illustrated in charts 4 to 7.

PYLORIC OBSTRUCTION

Chart 4 illustrates changes found in the blood of a dog during five days following pyloric obstruction. Here again is demonstrated a striking reciprocal relation between changes of chloride and diphosphoglycerate in the blood cells.

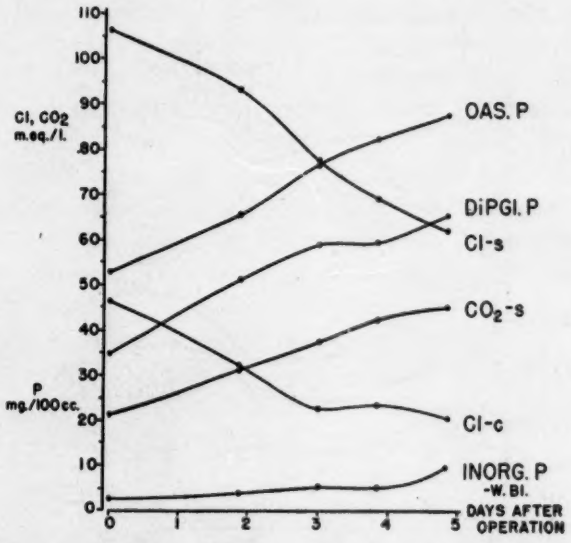


Chart 4.—Changes in the blood of a dog following pyloric obstruction. (For explanation of abbreviations see chart 2.)

In this condition, as is well known, losses of chloride from the body by vomiting lead to progressive decreases of chloride in the blood, only partly compensated by increases of bicarbonate. The decreases of chloride in serum and cells and increases of carbon dioxide in the serum shown in chart 4 are typical of findings commonly noted during this condition. In similar experiments, Guest and Andrus[13] previously found that large increases in the concentration of organic acid-soluble phosphorus in the blood cells accompanied the decreases in concentra-

13. Guest, G. M., and Andrus, W. DeW.: Chemical Studies of Blood in High Intestinal Obstruction: Distribution of Phosphorus and Intracellular Changes, J. Clin. Investigation **11**:455, 1932.

tion of chloride in the cells. Such changes again are demonstrated in chart 4, and here the increases of organic acid-soluble phosphorus are closely accounted for at each stage by the parallel increases in the diphosphoglycerate.

In their earlier studies Guest and Andrus [18] also showed that in dogs with intestinal obstruction the parenteral administration of a physiologic solution of sodium chloride prevented the increases of organic acid-soluble phosphorus in the blood cells as well as preventing the decreases of chloride in the blood and the development of alkalosis.

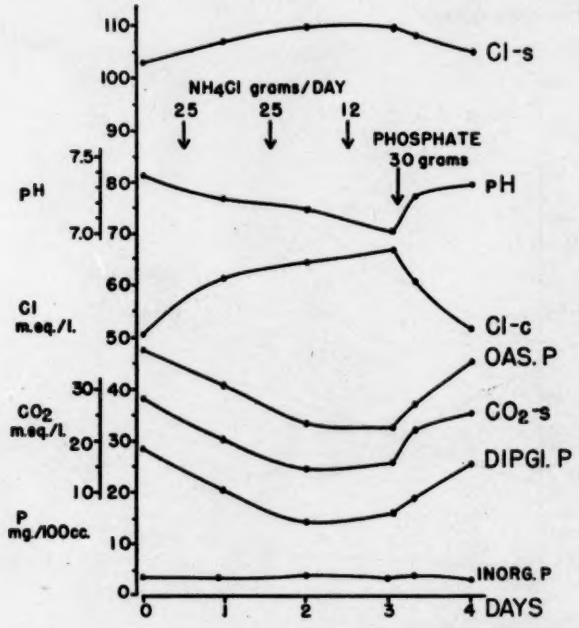


Chart 5.—Changes in the blood of a man during the development of acidosis induced by the ingestion of ammonium chloride and during recovery, after the ingestion of sodium and of potassium phosphate. (For explanation of abbreviations see chart 2.)

AMMONIUM CHLORIDE ACIDOSIS

Chart 5 demonstrates changes found in blood cells and serum during the development of and recovery from ammonium chloride acidosis. This was a self experiment by one of us (S. R.), who took by mouth 25 Gm. of ammonium chloride on two successive days and 12 Gm. the third day. (The substance was taken in divided doses in enteric-coated tablets.) Immediately after the sample of blood was taken, at the end of the third day, 30 Gm. of a mixture of sodium phosphate and potassium phosphate was ingested. During the three day period in which

the ammonium chloride was taken, there was a marked increase of chloride in both serum and cells, the carbon dioxide content of the serum decreased nearly to half its initial level, and the p_H decreased from 7.37 to 7.06. During the development of acidosis the concentration of organic acid-soluble phosphorus in the cells decreased from 48 to 32 mg. per hundred cubic centimeters, and this change was almost exactly accounted for in the diphosphoglycerate fraction.

Similar decreases in the concentration of organic acid-soluble phosphorus in the blood cells in ammonium chloride acidosis were first demonstrated by Haldane,[14] also in a self experiment. Haldane found that such acidosis as that just described, if left untreated, required seven to ten days for full recovery. This was found also by Rapoport [15] in a previous experiment, when he first identified these changes of the organic acid-soluble phosphorus in the diphosphoglycerate fraction. Here, however, as shown in chart 5, the ingestion of the phosphate was followed by rapid recovery, partly demonstrable after five hours and complete after twenty-four hours.

During the three day period of development of acidosis, the excretion of both phosphorus and chloride in the urine increased to more than double the normal rate. During the two days following ingestion of phosphate the urinary excretion of chloride decreased to considerably less than normal.

This and other observations have led to the clinical trial of phosphate solutions in the treatment of certain types of acidosis. An example of an infant so treated is cited in the next paragraph, and more data on this subject will be reported later.

ACIDOSIS OF GASTROENTERITIS

Chart 6 illustrates changes found in the blood of a 1 month old infant with severe acidosis and dehydration due to enteritis of undetermined cause. The condition was attended with marked diarrhea but no vomiting. Stool cultures yielded no dysentery bacilli. In the chart are represented data from blood analyses made daily or every second day during eleven days of the recovery period. The use of micromethods permitted these studies to be made on 2 and 3 cc. samples of blood.

---

14. Haldane, J. B. S.; Wigglesworth, V. B., and Woodrow, C. E.: Effect of Reaction Changes on Human Inorganic Metabolism, Proc. Roy. Soc., London, s.B **96**:1, 1924-1925.

15. Rapoport, S.: Ueber Phosphorglycerinsäure als Transportsubstanz des Blutphosphors und ihr Verhalten bei experimenteller Ammonchloridazidose, Biochem. Ztschr. **289**:411 and 416, 1937.

In the first samples of blood examined, the carbon dioxide content of the serum was 3.5 milliequivalents per liter; the chloride concentration was high in both serum and cells, the high ratio of the chloride in the cells to the chloride in the serum indicating a very low p_H, and the concentration of organic acid-soluble phosphorus in the cells was reduced to 30 mg. per hundred cubic centimeters.

The curves demonstrate changes in concentrations of chloride in the serum and the cells, carbon dioxide in the serum and organic acid-soluble phosphorus in the cells in the blood of this infant during eleven days. With adjustments of the carbon dioxide and the chloride to normal concentrations, the concentration of organic acid-soluble phos-

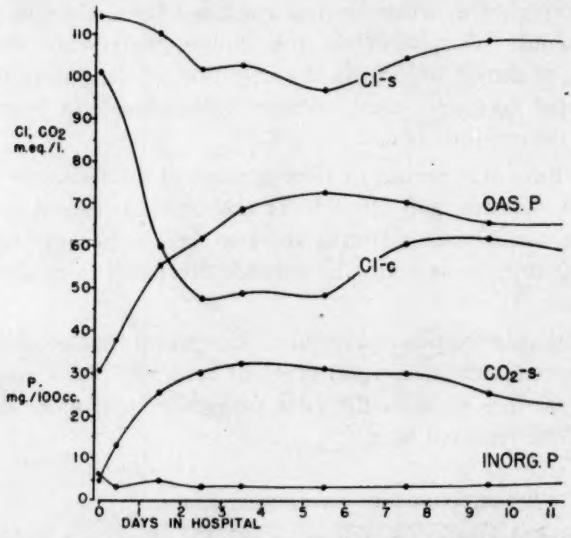


Chart 6.—Changes in the blood of a 1 month old infant during recovery from severe acidosis due to gastroenteritis. (For explanation of abbreviations see chart 2.)

phorus in the cells rose progressively, reaching a concentration higher than normal, and then returned to normal.

As treatment, the infant received salt and dextrose solutions by continuous intravenous drip and a blood transfusion on the third day. Sodium bicarbonate solution was given intravenously the first and second days in doses calculated to correct the acidosis, but only half the expected increase in serum carbon dioxide was obtained the first day. A phosphate solution was given by mouth the second and third days; this therapy was stopped at the end of the third day, when the organic acid-soluble phosphorus in the cells reached a normal concentration.

DIABETIC ACIDOSIS

Chart 7 illustrates changes in the blood in the severe acidosis of diabetic coma and during recovery from this condition. These observations were made on an adult patient of the medical service of the Cincinnati General Hospital, whom we studied with the permission of Dr. M. Blankenhorn and Dr. C. A. Mills. The patient had been in coma for several hours before she was brought to the hospital and the first observations were made.

In the first sample of blood, drawn before treatment was started, the carbon dioxide content of the serum was 3.8 milliequivalents per liter and the p_H was 6.84; the concentration of chloride in the serum was

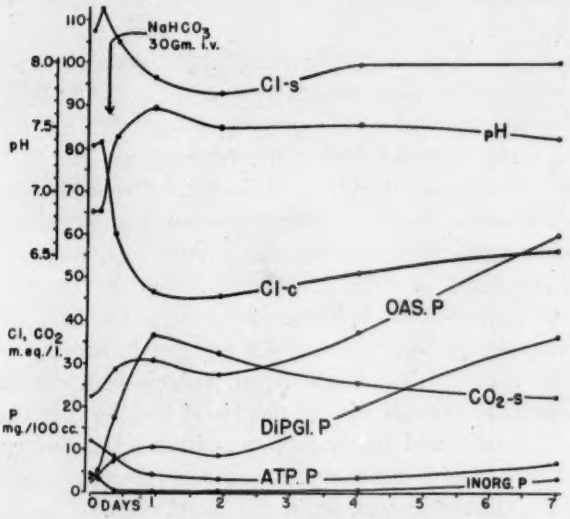


Chart 7.—Changes in the blood of a woman during recovery from the severe acidosis of diabetic coma. (For explanation of abbreviations see chart 2.)

107 milliequivalents and in the cells 80 milliequivalents per liter. The concentration of organic acid-soluble phosphorus in the cells was 22 mg. per hundred cubic centimeters, and the concentration of diphosphoglycerate was too low for estimation—less than 3 mg. per hundred cubic centimeters and probably 0.

Initial treatment consisted in the administration of insulin and the continuous intravenous injection of a physiologic solution of sodium chloride. After three hours, the p_H of the blood serum was unchanged and the other values showed only slight changes. After six hours, when the findings for the second sample of blood were noted, 30 Gm. of sodium bicarbonate was given intravenously. Two hours after the

sodium bicarbonate solution was administered, the level of serum carbon dioxide was found to be increased to 17 milliequivalents per liter and the p_H to 7.43. Twelve hours later (i. e., twenty-two hours after the first sample of blood was taken) the carbon dioxide content of the serum was found to be increased still further, to 37 milliequivalents per liter, and the p_H to 7.65. Subsequently the carbon dioxide and p_H values gradually fell to normal. The curves representing organic acid-soluble phosphorus and diphosphoglycerate concentrations in the cells followed courses parallel to each other, rising in the first twenty-two hours, then falling slightly at forty-eight hours and thereafter gradually rising to normal levels. The patient's clinical condition appeared to be fairly well restored to normal after forty-eight hours, but even at the end of the fourth day the values for organic phosphorus in the blood cells were still abnormally low.

The changes of inorganic phosphorus and adenosinetriphosphate, which are closely parallel, deserve special attention. In the first twenty-four hours the concentration of inorganic phosphorus in the serum decreased to 0.6 mg. per hundred cubic centimeters and in the cells decreased to 0. (The curve "INORG. P" in chart 7 represents inorganic phosphorus in the whole blood.) During the same period the concentration of adenosinetriphosphate phosphorus in the cells decreased from 12 to 6.6 mg. per hundred cubic centimeters. On the fourth day the concentration of inorganic phosphorus in the cells was still 0, and of adenosinetriphosphate phosphorus only 4.8 mg. per hundred cubic centimeters. On the seventh day, however, all values were normal. The decrease of inorganic phosphorus in the blood can be ascribed partly to the effects of insulin and partly to concomitant effects of correcting the acidosis—effects which favor the resynthesis of organic phosphorus compounds in the tissues as well as in the blood cells.

During this period striking changes in the urinary excretion of phosphorus were found. During the first four hours the rate of phosphorus excretion in the urine was extremely high, but during the next twelve hours it decreased rapidly, and in the second twenty-four hour period practically no phosphorus was found in the urine. The urinary excretion of phosphorus was negligible throughout the remainder of the seventh day period represented in the chart but was normal on the tenth day.

These changes in the urinary excretion of phosphorus, together with the fact that the concentration of organic acid-soluble phosphorus in the blood cells increased so slowly, suggest that the labile phosphorus reserves of the patient had been exhausted by increased excretion during the period of acidosis. During the period of recovery, the resynthesis of the organic phosphorus compounds in the blood and presumably also in the tissues kept the concentration of both inorganic phosphorus and

adenosinetriphosphate phosphorus in the cells very low until the diphosphoglycerate was restored and a certain equilibrium was reached between supply and demand.

Further studies are being made to see whether under such conditions the administration of phosphate will hasten recovery from diabetic acidosis and hasten the restoration of the organic phosphorus compounds in the blood cells to normal.

TABLE 1.—*Concentrations of Anions and Cations in Blood Cells of a Dog Before and After Pyloric Obstruction*

	Before Obstruction, mEq. per Kg. Water	2 Days After Obstruction, mEq. per Kg. Water
Chloride	65.3	23.5
Bicarbonate	16.8	22.0
Hemoglobin	41.8	37.5
Inorganic phosphorus	1.2	4.5
Diphosphoglycerate	33.5	65.4
Other organic phosphorus	9.4	11.4
Sum of anions	168.0	164.3
Inorganic cations	163.6	169.2

TABLE 2.—*Concentrations of Anions and Cations in Human Blood Cells During Diabetic Acidosis and During Recovery* *

	During Coma, mEq. per Kg. Water	During Recovery: First Day, mEq. per Kg. Water	During Recovery: Seventh Day, mEq. per Kg. Water
Chloride	114.7	65.6	83.3
Bicarbonate	4.7	30.1	16 9
Hemoglobin	4.9	51.2	33.6
Inorganic phosphorus	2.4	0	2.0
Diphosphoglycerate	±0	10.4	36.5
Other organic phosphorus	11.0	14.2	15.7
Ketone acids	±11.8	±1.1	0
Sum of anions	149.5	172.6	188.0
Inorganic cations	140.1	175.3	189.0

* These samples of blood are the first, fourth and seventh (last) represented in figure 8.

ELECTROLYTE EQUILIBRIUM OF THE BLOOD CELLS

The data presented in tables 1 and 2 show the close agreement that may be obtained between the total anions and the total inorganic cations of blood cells when the organic phosphorus compounds are taken into account. The anion equivalencies of diphosphoglycerate in these samples of blood were calculated from existing data [16] on the titration curve of

16. Rubin, S. H.: Determination of the Buffer Alkali in Cutaneous Blood, J. Biol. Chem. **126**:679, 1938. Kiessling, W.: Ueber die Titrationskurven einiger 3-Kohlenstoff-Phosphorsäuren Ester und der Inosinpyrophosphorsäure, Biochem. Ztschr. **273**:103, 1934.

this substance. "Other organic phosphorus" includes the organic acid-soluble phosphorus not determined as diphosphoglycerate. Values assigned to this unidentified fraction were based on the titration curve of adenosinetriphosphate.[17] While this fraction is known to include other compounds (mainly hexosephosphates), the error introduced by assuming it to be all adenosinetriphosphate is small. The equivalency of hemoglobin was calculated according to data of Hastings and co-workers [18] on dog's hemoglobin and data of Adair [19] on human hemoglobin. The bicarbonate values were corrected for carbamate carbon dioxide [20] and for free carbonic acid.

In the two columns of table 1 are listed the concentrations of anions and inorganic cations (total base) in the cells of samples of blood drawn from a dog before and two days after pyloric obstruction. The changes found in the second sample are similar to those illustrated in chart 3. The sums of the anions in each column differ from the values for the inorganic cations by only plus or minus 3 per cent, and the diphosphoglycerate is shown to be the most important anion compensating for the decrease of chloride in the cells.

In table 2 are listed the concentrations of anions and cations in the cells of 3 of the samples of blood drawn from the diabetic patient represented in figure 7. The samples were drawn respectively before treatment was started, one day later and seven days later (the first, fourth and seventh samples shown in figure 7). In calculating the equivalencies of the ketone acids, it was assumed that B-hydroxybutyric acid made up 65 per cent of the total ketones determined in the first sample and 75 per cent of the ketones in the second sample. In calculating the anion equivalency of the hemoglobin in all samples (venous blood) it was assumed that the oxygen saturation was 50 per cent. The oxygen content of the blood as drawn was not determined in these samples, as it was in the samples represented in table 1. The saturation was probably less than 50 per cent in the first sample and more in the

---

17. Lohmann, K.: Untersuchungen zur Konstitution der Adenylpyrophosphorsäure, Biochem. Ztschr. **254**:381, 1932.

18. Hastings, A. B.; Van Slyke, D. D.; Neill, J. M.; Heidelberger, M., and Harington, C. R.: Studies of Gas and Electrolyte Equilibria in Blood: V. Acid Properties of Reduced and Oxygenated Hemoglobin, J. Biol. Chem. **60**: 89, 1924.

19. Adair, G. S.: The Hemoglobin System: V. Relation of Hemoglobin and Bases, J. Biol. Chem. **63**:517, 1925.

20. Ferguson, J. K. W.: Carbamino Compounds of CO_2 with Human Hemoglobin and Their Role in Transport of CO_2, J. Physiol. **88**:40, 1936. Stadie, W. C., and O'Brien, H.: The Carbamate Equilibrium: II. Equilibrium of Oxyhemoglobin and Reduced Hemoglobin, J. Biol. Chem. **117**:439, 1937. Dill, D. B.; Edwards, H. T., and Consolazio, W. V.: Blood as Physiochemical System: Man at Rest, ibid. **118**:635, 1937.

others. While these assumptions introduce some uncertainties, such calculations adequately serve the purpose of the present discussion. In this example of diabetic acidosis, the decrease in concentration of diphosphoglycerate is seen to be the most important adjustment compensating for the increases of chloride and other anions in the blood cells. The values for total base, low in the first sample and high after recovery, are typical of values which we have found in other cases. These data will be reported more fully in later communications.

COMMENT

These observations emphasize the importance of several functions of the organic acid-soluble phosphorus compounds of the red blood cells. Their participation in carbohydrate metabolism has been described by various investigators who have studied their role in the glycolytic process. Less attention, however, has been paid to other functions of these compounds, which are suggested more or less clearly by the results of the studies reported here.

That these compounds constitute a phosphorus reserve of considerable importance is suggested especially by the observations on rickets and acidosis. In rats given the high calcium, low phosphorus diet the concentration of organic acid-soluble phosphorus in the blood cells decreased gradually during the period of phosphorus deficiency and the development of the rachitic condition. The findings during acidosis suggest that the well known increase of phosphorus excretion in the urine in this condition comes partly from the diphosphoglycerate of the blood cells. The slow return to normal concentration of the organic acid-soluble phosphorus compounds during recovery from diabetic acidosis, when this reserve and probably also that in other tissues was exhausted, has been noted in the description of chart 7. In these conditions, therefore, the concentration of diphosphoglycerate in the blood cells appears to be an index of the state of the body with regard to total amounts of labile phosphorus available.

Great lability of this reserve store of organic acid-soluble phosphorus compounds in the blood cells in abnormal circumstances is easily demonstrable in conditions such as those which have been cited here. This was also previously demonstrated in experiments dealing with the effects of large doses of viosterol in rabbits [2] and in studies of the decomposition of diphosphoglycerate in acidified blood in vitro.[4] Evidence that the organic acid-soluble phosphorus compounds of the blood cells are normally in a state of flux, being continuously decomposed and resynthesized, has been reported recently by Hevesy,[21] who studied the fate of

21. Hevesy, G.: The Application of Isotropic Indicators in Biological Research, Enzymologia **5**:138, 1938.

radioactive phosphorus taken up by normal blood cells. In a normal human being and in a normal rabbit, radioactive phosphorus injected intravenously was rapidly transferred from the plasma to the organic phosphorus compounds of the blood cells. Two hours after the injection, a considerable part of the organic phosphorus in the blood cells was found to be replaced by the "labeled" phosphorus. Such findings suggest that there is a continuous passage of inorganic phosphorus to and fro between cells and plasma and that in the cells there occur continuous esterification of inorganic phosphorus and hydrolysis of organic phosphorus compounds. Hevesy's data indicate that through such processes the organic phosphorus compounds in the cells may be completely rejuvenated (i. e., decomposed and resynthesized) in twenty-four hours or less.

In addition to acting as a labile phosphorus reserve, the organic acid-soluble phosphorus compounds probably serve as intermediary transport substances for the transfer of phosphorus to serve various needs of the body. The fact that the increased excretion of phosphorus in the urine in acidosis is accompanied by a decrease in the concentration of diphosphoglycerate in the blood cells suggests that this substance may act as a transport for phosphorus destined to be excreted by the kidneys. The fact that the concentration of diphosphoglycerate in the blood cells increases after suppression of renal function also may be cited as indirect evidence that this substance has such a function. The fact that the concentrations of organic phosphorus compounds in the blood cells of rats who were receiving a rachitogenic diet were closely related to the processes of development and healing of rickets may be placed in the same category of indirect evidence that these compounds serve as transport substances, in this case for phosphorus needed in ossification. Robison and co-workers [22] have suggested that phosphorus utilized in bone passes through an intermediate esterification before it is assimilated by ossifying cartilage. An intermediate esterification of phosphorus in the blood also may serve in the transport of phosphorus destined for bone formation.

The importance of organic acid-soluble phosphorus compounds as nondiffusible anions in the blood cells has been the subject of much conjecture. In 1923, when Van Slyke, Wu and McLean [23] summed up the then determinable anions and cations in horse blood cells and

---

22. Robison, R., and Rosenheim, A. H.: Calcification of Hypertrophic Cartilage in Vitro, Biochem. J. **28**:684, 1934. Robison, R.; MacLeod, M., and Rosenheim, A. H.: Possible Significance of Hexosephosphoric Esters in Ossification: Calcification in Vitro, ibid. **24**:1927, 1930.

23. Van Slyke, D. D.; Wu, H., and McLean, F. C.: Studies of Gas and Electrolyte Equilibria in the Blood: V. Factors Controlling the Electrolyte and Water Distribution in the Blood, J. Biol. Chem. **56**:765, 1923.

found a considerable anion deficit, they suggested that this deficit probably lay in the unidentified phosphate esters. Others also have found variable anion deficits in similar studies of human blood cells in different conditions. The data presented in tables 1 and 2 confirm the surmise of Van Slyke, Wu and McLean and show that the most important of the phosphate esters, as an anion in the cells, is the diphosphoglycerate. The anion equivalency of diphosphoglycerate in human and in dog blood cells is normally around 30 milliequivalents per kilogram of water; in pathologic conditions its concentration may decrease nearly to 0 or increase to more than double the original amount. Through these changes, the diphosphoglycerate compensates for wide alterations in concentration of other anions and plays an important part in maintaining a state of equilibrium between the cations and anions of the cells.

The influence of diphosphoglycerate, as a nondiffusible anion in the red cells, on the Donnan equilibrium will be treated elsewhere. Let it suffice to report here that the theoretic ratios for the distribution of the diffusible ions Cl^-, HCO^-_3 and H^+, calculated from observed concentrations of diphosphoglycerate and hemoglobin in the cells, agree closely with ratios actually observed in normal states and in the conditions of acidosis and alkalosis here described.

Again it should be noted that all such changes of diphosphoglycerate depend on reactions of the glycolytic cycle and on various factors which influence those reactions. These findings thus bring the glycolytic process—an enzymatic system—into close relation with other mechanisms concerned in adjustments of the acid-base equilibrium of the blood.

CONCLUSIONS

The organic acid-soluble phosphorus compounds of the red blood cells constitute a labile phosphorus reserve of considerable consequence, serving diverse functions. Readily synthesized and decomposed in the blood through reactions of the glycolytic cycle, these compounds participate in carbohydrate metabolism and also in the transfer of phosphorus in the body for other anabolic and catabolic processes. As nondiffusible anions in the cells, they play an important part in the maintenance of the acid-base equilibrium of the blood. The most important of these compounds, both in its normal concentration and in the magnitude of its changes in pathologic conditions, is the diphosphoglycerate. The concentration of diphosphoglycerate in the blood cells is increased after impairment or suppression of renal function and after pyloric obstruction; it is decreased in rickets, in ammonium chloride acidosis, in acidosis in infants with gastroenteritis and in diabetic acidosis.

News and Comment

GENERAL

Directory of Medical Specialists.—The first edition of the *Directory of Medical Specialists,* listing approximately 14,000 specialists certified by the twelve American boards and the two affiliate boards in the specialties, will be issued by the Advisory Board for Medical Specialties in December. It will be the official publication of the American Board for Medical Specialties and will contain, without expense to them, only the names of those specialists who have been certified by the American boards. It is expected that the directory will be issued every two years.

The directory will contain three sections: (1) a brief description of the Advisory Board for Medical Specialties, its organization and its objectives; (2) a description of the individual boards, with a geographic and a detailed biographic listing of their diplomates, the requirements for admission to their examinations for certification, the details of their organization and other general information, and (3) a complete alphabetic list of all 14,000 diplomates, with their addresses and indications of certification in their specialties.

The editorial board consists of the secretaries of the fourteen American boards. Dr. Paul Titus, 1015 Highland Building, Pittsburgh, secretary of the Advisory Board for Medical Specialists, is the directing editor.

The project is not designed to be profit making; hence the subscription price has been set at $3.50 a copy, which is computed to cover only publication expenses. Subscriptions may be sent to the publication office of the Columbia University Press, 2960 Broadway, New York, or to the office of the directing editor.

PERSONAL NEWS

Dr. John G. Young Selected.—Dr. John G. Young has been selected chief of staff of the new Texas Children's Hospital at Dallas, which is now under construction.

DEATHS

Dr. Howard B. Hamilton, professor emeritus of pediatrics at the University of Nebraska, died of coronary thrombosis on October 12, at the age of 64 years.

SOCIETY NEWS

University of Michigan Pediatric and Infectious Disease Society.—The University of Michigan Pediatric and Infectious Disease Society will hold its next meeting at Ann Arbor on Nov. 24 and 25, 1939.

UNIVERSITY NEWS

Appointments.—Dr. Albert B. Sabin, formerly associate of the Rockefeller Institute for Medical Research, has taken up his new duties as associate professor of pediatrics at the University of Cincinnati and fellow of the Children's Hospital Research Foundation. Dr. Sabin will continue his studies on viruses and the filtrable micro-organisms of the pleuropneumonia group.

Dr. Sabin will have several assistants, among them Dr. Joel Warren, formerly in the department of bacteriology of Columbia University, who will be a research associate in the Children's Hospital Research Foundation.

Dr. Sabin will receive the Theobald Smith Award of the American Association for the Advancement of Science at its annual winter meeting.

Dr. Parker Dooley, assistant professor of pediatrics at the Cornell University Medical College and associate attending pediatrician at the New York Hospital, has been appointed assistant professor of pediatrics at the University of Chicago.

Notices

CUMULATED INDEX OF THE AMERICAN JOURNAL OF DISEASES OF CHILDREN

Requests have been received for a twenty year index of the AMERICAN JOURNAL OF DISEASES OF CHILDREN. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed $6 a copy; that is, whether one thousand copies could be sold. It will be appreciated if those who are interested in such an index will fill out and send the form which appears below to the Managing Editor at the publication office, 535 North Dearborn Street Chicago.

I SHOULD BE WILLING TO SUBSCRIBE TO A CUMULATED INDEX OF THE AMERICAN JOURNAL OF DISEASES OF CHILDREN AT $6.00.

NAME .....

ADDRESS .....

.....

DATE.....

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

Effect of Apples and Cranberries on Calcium Retention. A. Mindell, W. B. Esselen Jr. and C. R. Fellers, Am. J. Digest. Dis. **6**:116 (April) 1939.

This experimental study on rats shows that both fresh cranberries and apples increase the body's retention of calcium.

Morrison, Savannah, Ga.

A Quantitative Study, by Means of Spectrographic Analysis, of Zinc in Nutrition. F. I. Scoular, J. Nutrition **17**:103 (Feb.) 1939.

The data are given from thirty-five studies of the zinc balances in 3 normal boys of preschool age. Spectrographic analysis of these diets showed the amount of zinc ingested to vary from 4 to 6 mg. The amount excreted in the urine was low (0.04 to 6 per cent of the zinc intake). The quantity passed in the feces was 2.016 to 6.624 mg. per day, showing some delay in excretion. On the basis of these findings Scoular suggests that 0.307 mg. of zinc per kilogram of body weight supplies the physiologic zinc needs of the preschool child.

Fredeen, Kansas City, Mo.

Studies of Fat-Free Diets. G. J. Martin, J. Nutrition **17**:127 (Feb.) 1939.

Martin presents data from a comparison of the average maximum growth of rats on a fat-free diet. He showed that their weight curve reached a subnormal plateau in four to five months. When methyl linoleate was given curatively (30 mg. daily), the second plateau occurred in six to twelve months; when it was given prophylactically, a plateau was reached in seven to nine months. Methyl linolenate was not an effective substitute for methyl linoleate. It was also noted that if a highly purified synthetic diet was used, complete in all dietary essentials, the weight curve reached a subnormal plateau, and responded to supplements of brain and liver. This was thought to be due to the growth-promoting factor of the arachidonic acid present in liver and brain tissue.

Fredeen, Kansas City, Mo.

A Long-Time Study of Nitrogen, Calcium and Phosphorus Metabolism on a Low-Protein Diet. B. L. Kunerth and M. S. Pittman, J. Nutrition **17**:161 (Feb.) 1939.

Three young women ate a constant low protein diet supplying 0.42 Gm. of protein per kilogram over a forty-five day period. Examination showed considerable fluctuation in their retention of nitrogen, calcium and phosphorus, with no definite cyclic tendency. The average nitrogen balance of each subject was positive when meat furnished 85 per cent of the nitrogen of the low protein diet. The fluctuations in retention of calcium and phosphorus tended to be parallel, but phosphorus was better utilized; all 3 subjects had on the average negative calcium balances and 2 had negative phosphorus balances.

Fredeen, Kansas City, Mo.

A Long-Time Study of Nitrogen, Calcium and Phosphorus Metabolism on a Medium-Protein Diet. M. S. Pittman and B. L. Kunerth, J. Nutrition **17**:175 (Feb.) 1939.

Four young women were given a constant diet furnishing 1.2 Gm. of protein (87.7 per cent from beef) and 40 to 45 calories per kilogram. This diet did not

eradicate the fluctuations in retention of nitrogen, calcium and phosphorus reported by the same authors when their subjects were given a low protein diet (A Long-Time Study of Nitrogen, Calcium and Phosphorus Metabolism on a Low-Protein Diet, *J. Nutrition* **17**:161 [Feb.] 1939). The medium protein diet maintained a positive balance of nitrogen and phosphorus during the forty-five consecutive balance days. The calcium balance remained negative, but an improvement in retention was noted over the period of the low protein study.

FREDEEN, Kansas City, Mo.

CALCIUM REQUIREMENTS OF FIVE PRE-SCHOOL GIRLS. J. OUTHOUSE, G. KINSMAN, D. SHELDON, I. TWOMEY, J. SMITH and H. H. MITCHELL, J. Nutrition **17**:199 (March) 1939.

This study indicated that the requirement of calcium for daily growth in these well nourished preschool girls was approximately 125 mg., with a standard deviation of ± 2.7; on the basis of body weight it was 7.5 ± 1.1 mg. per kilogram. The maximum average calcium retentions, ranging from 84 to 154 mg., were attained on a calcium intake not greatly in excess of 600 mg. daily. These investigators agree with others that a pint of milk daily is sufficient for the calcium needs.

FREDEEN, Kansas City, Mo.

UTILIZATION OF CARBOHYDRATE IN HUMAN UNDERNUTRITION. M. W. JOHNSTON, J. M. SHELDON and L. H. NEWBURGH, J. Nutrition **17**:213 (March) 1939.

These investigators conclude that the carbohydrate stores of the body are replenished before carbohydrate is used as fuel. Their work was done on 2 normal men in a respiration chamber. They were fed a diet low in calories and varying amounts of carbohydrates so as to deplete their glycogen stores. Diminished oxidation of carbohydrate was noted even though the diet was below caloric requirements. This failure to oxidize all the ingested carbohydrate appeared to be related to the degree of depletion of the glycogen stores.

FREDEEN, Kansas City, Mo.

ENERGY CONTENT OF GOAT MILK. V. E. PETERSON and C. W. TURNER, J. Nutrition **17**:293 (March) 1939.

Peterson and Turner show that the energy value of goat milk can be estimated with considerable accuracy from the protein, lactose and fat percentages or from the percentages of total solids. An average energy value of 342.28 calories for 1 pound (453 Gm.) of 4 per cent goat's milk was found in comparison with 343.66 calories for the same amount of cow's milk.

FREDEEN, Kansas City, Mo.

CALCIUM REQUIREMENTS OF INFANTS AND CHILDREN. K. KLINKE, Med. Klin. **34**:117 (Aug. 26) 138.

Because of numerous factors which may influence the absorption and metabolism of calcium, it is difficult to determine the calcium requirement. The breast-fed infant receives about 0.05 Gm. per kilogram during the first three months and about 0.55 Gm. daily at the sixth month. The artificially fed infant has a higher calcium intake and may retain more.

For older children 0.5 Gm. daily is adequate. Even if no milk is fed, the requirement can be met readily.

Klinke discusses the various disorders characterized by an actual or probable disturbance of calcium metabolism.

SIEMSEN, Chicago.

COLOSTRUM BODIES. P. FORSSELL, Monatschr. f. Kinderh. **77**:215 (Feb.) 1939.

This is a review of the literature concerning the microscopic bodies found in colostrum by Donne in 1837. Forssell describes two different objects found in colostrum. The original Donne colostrum bodies are probably not cellular elements, as no nucleus can be demonstrated by staining. But very large nucleated cells can be demonstrated with methylene blue and May-Grünwald-Giemsa stains, which are probably leukocytes.

GERSTLEY, Chicago.

MINERAL AND WATER METABOLISM IN EARLY INFANCY AND ITS RELATION TO THE PROBLEM OF ARTIFICIAL FEEDING. TOPIC II. THE FOURTH INTERNATIONAL PEDIATRIC CONGRESS, ROME, SEPTEMBER 1937. Acta pædiat. **22**:73, 1938.

The condensed version of the papers that were read under this heading and of the discussion that they provoked fills 94 pages. The topic is introduced by a brief and singularly lucid interpretation by McQuarrie of the "Significance of Body Water and Certain Electrolytes in Infant Nutrition." Toverud reviews certain aspects of her work on the relation between the diet of the mother and the mineral and vitamin stores of the infant at the time of birth. Fanconi adds the description of another clinical species, "diabetes insipidus occultus," to the considerable list of descriptions of newly noted conditions of which he is the author. Chwalibogowski reports on some extremely interesting experiments by which it was shown to be possible to procure satisfactory growth and development of infants with diets containing either little or no fat or a much reduced content of carbohydrate. Sodium, chlorine, calcium and phosphorus receive the largest amount of attention but sulfur, iodine and copper are also considered. Many of the papers are published in Italian.

MCCUNE, New York.

Vitamins; Avitaminoses

HISTOLOGICAL STUDY OF HYPERVITAMINOSIS D: THE RELATIVE TOXICITY OF THE VITAMIN D OF IRRADIATED ERGOSTEROL AND TUNA LIVER OIL. R. S. HARRIS, B. D. ROSS and J. W. BUNKER, Am. J. Digest. Dis. **6**:81 (April) 1939.

Experimental study showed that histologic changes occur in the kidney, stomach, heart, aorta and lung of the rat when 5,000 times the therapeutic dose of vitamin D is given, whether irradiated ergosterol or tuna liver oil is used.

MORRISON, Savannah, Ga.

SCORBUTIC SUBPERIOSTEAL HEMORRHAGE COMPLICATED BY OSTEOMYELITIS AND PYARTHROSIS. E. SHAPIRO and M. MORRIS, Arch. Pediat. **55**:465 (Aug.) 1938.

In a 9 month old boy rickets and scurvy developed, complicated by osteomyelitis. The scorbutic process was progressive in spite of what was considered adequate therapy with vitamin C.

ORR, Buffalo.

THE OXYGEN UPTAKE OF TISSUES IN VITAMIN DEFICIENCIES. B. SURE and J. B. DEWITT, J. Biol. Chem. **126**:287, 1938.

Measurements of the oxygen uptake of several tissues of albino rats were made by Sure and DeWitt with the Barcroft apparatus. The experiments were carried out by the paired feeding method, the daily food intake of the animals that served as controls having been restricted to the same plane of nutrition as that of the pathologic litter mates during the previous twenty-four hours. The results, expressed as the percentage of reduction in oxygen uptake, are summarized as follows: Deficiency of vitamin B complex: kidney (21 groups), 15 per cent; heart (9 groups), 18 per cent. Vitamin B_1 deficiency associated with polyneuritis: cerebrum (16 groups), 16 per cent; heart (14 groups), 17 per cent; kidney (19

groups), 19 per cent. Vitamin A deficiency: cerebrum (13 groups), 14 per cent.; heart (7 groups), 19 per cent. The quantitative reduction in oxygen uptake of the kidney, heart or cerebrum of the albino rat given a diet deficient in vitamin B complex, vitamin B_1 or vitamin A was not influenced by the extent of loss of weight, severity of polyneuritis or severity of ophthalmia, respectively.

PAGE, Indianapolis. [ARCH. NEUROL. & PSYCHIAT.]

DIET AND RATE OF DEPLETION OF HEPATIC VITAMIN A. E. J. LEASE and H. STEENBOCK, J. Nutrition **17**:85 (Jan.) 1939.

The rate of loss of vitamin A from the liver was not affected by the amount or the rancidity of the fast given. Nor was it affected by the rapid depletion of fat from the liver or administration of choline. FREDEEN, Kansas City, Mo.

THE BIOLOGICAL VALUE OF CAROTENE IN VARIOUS FATS. E. J. LEASE, J. G. LEASE, H. STEENBOCK and C. A. BAUMANN, J. Nutrition **17**:91 (Jan.) 1939.

When rats were fed various fats supplemented with 1 microgram of carotene daily, they showed inferior growth. The fats used were triolein, linseed oil and "refined" peanut oil. Equal growth responses were noted when cottonseed oil, soybean oil, lard, decolorized butter fat, coconut oil and crude peanut oil were fed supplemented with carotene in the same manner. These authors proved that there were marked increases in the liver stores of vitamin A from the administration of either carotene or vitamin A, regardless of the kind of fat in the basal diet of the rat. The rate of cure of ophthalmia was essentially the same on all oils.

FREDEEN, Kansas City, Mo.

A STUDY OF BREED AND SEASONAL VARIATIONS IN THE ASCORBIC ACID CONTENT OF CERTIFIED MILK FROM GUERNSEYS AND HOLSTEINS. A. D. HOLMES, F. TRIPP, E. A. WOELFFER and G. H. SATTERFIELD, J. Nutrition **17**:187 (Feb.) 1939.

These authors conclude that the ascorbic acid content of raw certified milk is high. The yearly average for Guernsey milk was 20.54 mg. per liter (17.76 to 23.37 mg. per liter); for Holstein milk, 18.17 mg. per liter (15.72 to 20.44 mg. per liter). Seasonal variation was noted, with peaks in February and late October.

FREDEEN, Kansas City, Mo.

A NOTE ON THE VITAMIN B_1–SPARING ACTION OF FAT. D. MELNICK and H. FIELDS JR., J. Nutrition **17**:223 (March) 1939.

Melnick and Fields conclude that when the fat content of the diet is increased, the metabolic requirement for thiamin (B_1) is decreased. Their chemical analyses indicate that lard contains no thiamin, so that the vitamin B_1–sparing action of fat is not due to administration of the vitamin. FREDEEN, Kansas City, Mo.

DISTRIBUTION OF VITAMIN B_1 (THIAMIN) IN MEAT AND MEAT PRODUCTS. O. MICKELSEN, H. A. WAISMAN and C. A. ELVEHJEM, J. Nutrition **17**:269 (March) 1939.

These Wisconsin investigators assayed by the rat growth method a variety of meats and meat products for vitamin B_1 content. Their results show a good percentage of thiamin in all meat and an exceedingly high percentage in pork muscle. In their discussion as to the practical applicability of this observation the authors conclude that a pork chop, even when fried, contains a day's supply of thiamin (325 international units of vitamin B_1).

A study as to stability of B_1 under various styles of cooking showed very slight destruction during frying but about 50 per cent destruction during roasting, broiling or stewing. FREDEEN, Kansas City, Mo.

VITAMIN-C DEFICIENCY AND PERIOSTITIS OF BOTH ULNAE? SCURVY. R. W. B. ELLIS, Proc. Roy. Soc. Med. **32**:139 (Jan.) 1939.

An infant aged 6½ months was brought to the hospital because of refusal of bottle, fretfulness and screaming of several weeks' duration. For two days the parents had noticed that the left forearm was swollen. The child had no orange juice. On examination both forearms were found to be swollen, the swelling involving both ulnas throughout their length. There was no beading of the ribs. There were no hemorrhages into the skin or mucosa. Physical examination otherwise gave negative results. Roentgenologic examination showed: (1) marked periostitis along practically the whole length of the shaft of each ulna, (2) no evidence of scurvy or rickets and (3) no abnormality in bones of the lower limbs. The infant was put on 2 oz. (62 cc.) of orange juice daily, which was taken well. He gained weight slowly but was difficult to feed. Roentgenograms taken of the ulnas six weeks later showed consolidation of the periosteal new bone, the appearance suggesting arrest of the condition and improvement. The report is accompanied by reproductions of roentgenograms of the ulnas, data on the investigations and a comment by the author.

WILLIAMSON, New Orleans.

THE PHOSPHORUS AND GLYCEROPHOSPHATASE OF THE BLOOD OF RACHITIC CHILDREN: VARIATIONS OBSERVED IN THE COURSE OF TREATMENT WITH ULTRAVIOLET RADIATION. E. LEENHARDT, J. BOUCOMONT and J. CAYLA, Rev. franç. de pédiat. **13**:144, 1937.

The authors studied the phosphorous, phosphate esters and phosphatase in the blood in a group of rachitic infants. They confirmed the opinion that in rickets the phosphorus is below 40 mg. per hundred cubic centimeters and that the lowering is due at least in part to diminution in the phosphate esters. The phosphatase content is usually about twice the normal. Treatment with ultraviolet radiation increased the phosphorus and phosphate esters. It also produced at the onset of treatment increase in the phosphatase. However, as treatment continued the latter dropped to normal levels.

LESLIE, Evanston, Ill.

FURTHER INVESTIGATIONS IN SINGLE DOSE VITAMIN THERAPY OF RICKETS. R. SCHIRMER and H. PETER, Monatschr. f. Kinderh. **75**:318 (Sept.) 1938.

This is a study of the vitamin D shock treatment of rickets in 61 children. It continues the studies of previous observers on the effects of a single massive dose of vitamin D. Case reports are given, with roentgenograms showing the results from the use of an average dose of 6 mg. of D_2. In complications of rickets, such as pneumonia, the authors gave as much as 10 to 15 mg. Decided improvement occurs in the rachitic picture as evidenced by the chemical composition of the blood, roentgenograms, electrical reactions and clinical manifestations in three days.

GERSTLEY, Chicago.

TREATMENT OF RACHITIC PATIENTS WITH VITAMIN D_3. H. WAGNER, Monatschr. f. Kinderh. **77**:1 (Jan.) 1939.

Studies have shown that vitamin D_2, obtained from irradiated ergosterol, has not the same effect as the vitamin D in cod liver oil. Recently vitamin D_3 has been obtained by irradiating cholesterol. Wagner contrasted the effects of D_3 with those of D_2 in 16 cases of rickets and found the former equally satisfactory.

GERSTLEY, Chicago.

CHANGES OF THE TEMPORAL BONE IN RICKETS AND IN "RENAL RICKETS." H. MELLER, Monatschr. f. Ohrenh. **72**:639 (July) 1938.

According to Meller, "renal rickets" is an endogenous form of rickets occurring in children after the sixth year of life. It is characterized by the fact that besides skeletal changes a chronic disease of the kidneys is present. The author had an opportunity to examine the petrous bones of a patient with this disease (a girl, 10½ years old). He observed the well known changes characteristic of rickets (extensive osteoid borders), particularly in the petrous apex, in the periosteal capsule of the inner ear and in the mastoid process, while the endochondral and the endosteal capsule evidenced almost no changes. Besides this he noted signs of *Knochenumbau* (rebuilding of bone) in the wall of the internal meatus and in the periosteal capsule of the inner ear, fibrosis of the marrow spaces and many osteoclasts. The last-mentioned observations characterize the microscopic picture of "renal rickets," while in ordinary rickets only the augmented osteoid borders and the osteoid in netlike arrangements, lying in the marrow and blood vessel spaces, are significant.

LEDERER, Chicago. [ARCH. OTOLARYNG.]

IS RICKETS DUE SIMPLY TO A VITAMIN DEFICIENCY? E. FÖLDES, Acta pædiat. **23**:178, 1938.

This is an exposition of a hypothesis relating to the cause and pathogenesis of rickets.

MCCUNE, New York.

Hygiene; Growth and Nutrition; Public Health

NUTRITION AS AFFECTED BY THE ECONOMIC LEVEL. G. E. ROBERTSON, Nebraska M. J. **24**:98 (March) 1939.

Suboptimal diets are widespread in all economic classes but especially in the low income groups. While deficiency diseases in manifest form are not frequent, subclinical deficiency states must occur more frequently than they are recognized. While the nutritional condition of a portion of the low income group has been improved through relief measures and dietary education, there are still many families whose food budgets are so low that an adequate diet is impossible. Such supplementary measures as free milk distribution and serving of school lunches have been of inestimable value in maintaining the nutritional position of the American child.

HAMILTON, Omaha.

SANITARY CONTROL OF MILK IN MONTREAL. A. BOLDUC, Union méd. du Canada **67**:724 (July) 1938.

Since 1925 regulation of the milk supply has been rigidly enforced. Every cow must be in good health and have a negative tuberculin reaction. Special milk or certified milk can be sold raw; all other milks must be pasteurized. Farms are inspected thoroughly at least once a year and are graded on a percentage of points basis. Any farm rating 80 per cent or over can sell "special milk." If the percentage falls below 49 per cent, or if the farmer will not make changes suggested by the inspectors, his milk is banned from the market. Other inspectors supervise the transportation and processing of milk and cream. The inspectors are checked by bacteriologic and chemical analyses in the laboratory. "Special milk" is allowed to contain 50,000 bacteria per cubic centimeter from June to September and 25,000 bacteria from October to May. Pasteurized milk must not contain more than 100,000 bacteria per cubic centimeter on delivery.

In 1935, 2,124 samples of pasteurized milk were tested. Only 20 (0.9 per cent) had a count of over 100,000; 1,660 (78.2 per cent) had less than 10,000. The

"special milks" showed 95.5 per cent conformity to regulation. Colon bacilli were absent in 89.8 per cent of the pasteurized samples and in 72.6 per cent of the "special" ones.

Biannual examination of employees and examinations of stools of handlers are done. Bottles from infected families are specially sterilized.

DAFFINEE, Boston.

SCHOOL LIFE AND AFTER FOR THE HANDICAPPED CHILD. W. A. DALEY, Proc. Roy. Soc. Med. **31**:1013 (July) 1938.

Daley in this paper on handicapped children deals only with those that can never be restored to mental or physical normality such as (1) mentally defective, (2) crippled, (3) deaf and partially deaf, (4) blind and partially sighted and (5) epileptic children. Parliament has required the social education authorities to provide special education for the blind and deaf since 1893 and for the mentally and physically defective since 1899. A brief account of the beginning of the provision for education and training of these children is given. Idiots and imbeciles are not discussed, for as soon as they are discovered they are dealt with by the mental deficiency acts, and they are discovered long before school age. Blind and seriously crippled children are found in the preschool period by the officers of the maternity and child welfare authorities and later by the school medical officers. A few general remarks are first made on the ascertainment of such children and their numbers, taking for the purpose London figures, as ascertainment is as complete there as anywhere in the country and there the special school service is well established and provides for every type of handicapped child. The author discusses fully the various types of handicapped children, under two groups:

1. The mentally defective. After these children have been examined and their deficiencies ascertained, they are placed in special schools known as M. D. Schools. The functions and routine of the schools are described in the paper, as are the acts of Parliament dealing with such children.

2. The physically defective. The analysis of the causes of the crippling of children (shown in the paper) shows a marked change. The most striking change has been the replacement of children crippled in their limbs by those crippled by heart disease. The proportion of cardiac cripples now in the special schools approaches 50 per cent of the total. The majority of these physically defective children attend the outpatient department of a hospital for supervision of treatment, and they are taken to and from school in an ambulance. They go to special schools known as P. D. Schools. A nurse is in daily attendance. The curriculum toward the end of school life is largely vocational. There is a special after-care association, subsidized by the Ministry of Labor to assist the head teachers in obtaining suitable employment for these children, and children from the P. D. Schools find lucrative posts. The Council also provides special schools for the deaf, the blind and the epileptic children. London has a unique range of hospital schools. These hospital schools are in the country or at the seaside. Here the children receive medical or surgical treatment under the most favorable conditions and at the same time continue their education. The author in giving results quotes from the "Health of the School Child," 1924: "Many of them, the blind, the deaf, and physically defective respond in an exceptional degree and become good and useful citizens able to compete with the normal; and even one-third to a half of the mentally defective are so much improved that they subsequently become contributory to their own independent maintenance and are safeguarded from most of the evils inherent in their condition."

WILLIAMSON, New Orleans.

Prematurity and Congenital Deformities

MATERNAL AND CHILD HEALTH SERVICES UNDER THE SOCIAL SECURITY ACT C. E. HAYES, West Virginia M. J. **35**:164 (April) 1939.

This is a rather lengthy descriptive discussion of the Social Security Act as it relates to maternal and child health services. Such information is given as should enable one to understand the aims, objects and purposes of the act as applied to maternal and child welfare.

The various phases of the subject are discussed under the following headings: "Administration of Service," "Scope and Content of Program," "Health Supervision Services," "Consultation Available (Obstetric and Pediatric)," "Postgraduate Courses" (refresher courses for rural physicians), "Nutritionists on Staffs" (state health departments), "Cooperation with Professional and Lay Groups" and "Unmet Needs."

SHAWKEY, Charleston, W. Va.

CONGENITAL ABNORMALITIES OF THE EXTREMITIES: THE HANDS. D. BROWNE, Practitioner **142**:270 (March) 1939.

Congenital absence of greater or lesser amounts of the tissues of the hand is common. The deficient member may vary from a simple stump ending the arm at the wrist joint to a hand with but one phalanx of a finger missing.

Even more frequent than the absence of normal digits is the presence of extra ones. These run from a minute lump of connective tissue with a covering of skin and almost invariably with a rudimentary nail at the tip to a finger fully formed and complete with active muscles and tendons. In every case removal is advisable.

Embryologically, the fingers should separate from one another by atrophy of the tissues which lie between them in the original limb bud. If this curious process fails, the result is syndactyly or webbed fingers. When two fingers are normal in every way except for being joined by skin, there is no doubt that they should be separated. But it must be clearly understood that there is only one way of doing this, and that is by supplying the missing surface between them from elsewhere on the body. There is no spare skin whatever in the hand, and the operations described in the textbooks for shifting flaps from the dorsum to the palmar surface and similar devices are not only inefficient but disastrous.

A peculiar congenital condition is ring constrictions of the fingers. These vary from a slight indentation of the skin to a complete amputation. They are usually considered to be the effect of pressure of "amniotic bands," though it is difficult to see how any band could produce a perfectly circular constriction of this sort; experiment with a roll of plasticine and a bit of string will show that it is possible in this way only to produce spiral marks. Streeter in 1930 brought forward much evidence to show that the condition is one of atrophy, analogous to the tropical disease called ainhum.

There is strong evidence that the tissues can be molded by pressure before birth just as they are well known to be afterward, in such instances as the deforming of feet by the Chinese or of infantile skulls by American and Egyptian tribes. It must be admitted, however, that the possibility of such an occurrence is usually dogmatically denied.

Another condition which may belong to this class is that curious syndrome of associated deformities of the hands and head known as acrocephalosyndactyly. If the developing limb buds were to become jammed against the skull in early fetal life, the result would be a mutual deformity of this kind, and the analogous cases in which the feet have obviously been impressed into the face or the cranium lend some probability to this hypothesis.

The variations of molding of the feet are infinite but fall into four main classes: (1) the "exaggerated normal" or calcaneovalgus; (2) metatarsal varus; (3) "external molding," "clubfoot" or equinovarus talipes; (4) irregular talipes.

GELSTON, San Francisco.

ON SPALDING'S SIGN OF INTRA-UTERINE DEATH OF THE FOETUS. E. C. FAHMY, Tr. Edinburgh Obst. Soc., 1938, p. 137; in Edinburgh M. J., November 1938.

Spalding's sign has been recognized generally as evidence of intrauterine fetal death. Fahmy reports a case in which some doubt arose as to the reliability of the sign, suggesting that loss of tissue fluids in the fetus may produce overlapping of the bones and weakening of the fetus, which, however, may still be alive. In the case reported the child was resuscitated at birth but succumbed about eight hours after delivery.

NEFF, Kansas City, Mo.

A CASE OF MASKED DOLICHOSTENOMELIA. C. RŒDERER, Bull. Soc. de pédiat. de Paris **36**:269 (April) 1938.

A girl 13½ years old presented some of the features of arachnodactyly.

BENJAMIN, Montreal, Canada.

BIOMETRIC STUDY OF GROWTH IN THE PREMATURE INFANT. P. GORINI, Lattante **9**:482 (Nov.) 1938.

Gorini reports comparative measurements on normal and premature infants at birth, at 6 months of age and at 12 months of age. At 12 months the premature infant becomes of the macrosplanchnic-brachycephalic type.

HIGGINS, Boston.

THE DEVELOPMENT OF PREMATURE INFANTS. W. SCHOBERLEIN, Monatschr. f. Kinderh. **76**:80 (Oct.) 1938.

This is a lengthy report of statistics collected in the Kaiserin Auguste Victoria-Haus, in Berlin. In the years 1920 to 1932, 776 premature infants were admitted; 337 survived, giving a mortality of 47.1 per cent. The article presents little that is not already known.

GERSTLEY, Chicago.

CONGENITAL DEFORMITIES OF THE SKELETON. I. BESDZIEK, Monatschr. f. Kinderh. **76**:305 (Dec.) 1938.

Besdziek reports on 3 children with decided skeletal deformities and gives roentgenograms. Two of the children were siblings. Their deformities were classified as dysostosis multiplex. The condition of the third child could not be diagnosed. The pictures show generalized hyperplastic change in the metaphyses of the long bones, ribs and also some of the shorter bones, as the vertebrae and shoulder blades. The patient showed other deformities, such as cleft palate, hernia and partial cryptorchidism.

GERSTLEY, Chicago.

CONSTITUTIONAL FACTORS IN THE ETIOLOGY OF PREMATURITY. T. BRANDER, Monatschr. f. Kinderh. **77**:11 (Jan.) 1939.

Of 376 premature births, 186 (49.5 per cent) resulted from complications during labor, such as toxicoses, infections and placental anomalies.

One and nine tenths per cent of the mothers suffered from hyperthyroidism, while 15 per cent showed thyroid enlargement.

In uncomplicated cases the smaller mothers tended more than the larger mothers toward premature labor.

The chief interest of the study lay in the observation that the tendency toward premature labor seems a familial affair, 28.6 per cent occurring in related groups against 12.8 per cent in the general population.

GERSTLEY, Chicago.

CORRELATION OF FETAL BODY LENGTH WITH THE WEIGHTS OF ORGANS. A. GIORDANO, Virchows Arch. f. path. Anat. **301**:380, 1938.

This is a correlation of body length with the weights of the heart, lungs, liver, spleen and kidneys according to accepted current methods of statistical analysis. This correlation is based on a study of 445 infants, dead at birth or shortly after birth, and varying in length from 30 to 67 cm. The females in the series numbered 199 and the males 246. A striking feature of this series is that 25 per cent of the infants had a body length of from 52 to 67 cm., indicating a duration of pregnancy beyond the normal limit. The high mortality in this group was due to intracranial hemorrhage. It suggests the advisability of terminating pregnancy at the normal term. The weights of the organs in the various length groups are given in tables and graphs. With lengths from 40 to 47 cm. and from 47 to 52 cm. the organ weights were practically the same for both males and females. In both males and females the rate of increase in organ weights was greater at body lengths of from 47 to 52 cm. than in younger fetuses, with lesser body lengths. With lengths from 52 to 67 cm., representing a prolonged duration of pregnancy, organ weights increased somewhat less rapidly, but the organ weights of males were decidedly greater than those of females in this group.

SCHULTZ, Chicago. [ARCH. PATH.].

EXPERIMENTS WITH WHEAT GERM OIL (VITAMIN E) IN THE NUTRITION OF PREMATURE INFANTS. F. WIDENBOUER, Ztschr. f. Kinderh. **60**:216 (Oct. 15) 1938.

Eleven of 17 premature infants whose weight had been stationary were given small amounts of wheat germ oil and showed a rapid gain in weight. Premature twins, serving as controls, were given olive oil also and showed a gain in weight. Widenbouer thinks his observations indicate a possible effect of vitamin E (olive oil also contains some vitamin E). Further investigations are in progress.

SIEMSEN, Chicago.

Newborn

INCLUSION BLENNORRHEA. A. E. BRALEY, Am. J. Ophth. **21**:1203 (Nov.) 1938.

This study was made to determine the pathologic changes in conjunctival and cervical tissues infected with the virus of inclusion blennorrhea and to localize the virus. The material for study was obtained from 8 infants with inclusion blennorrhea and from the mothers of 6 of the 8. Braley makes these conclusions:

"1. The inclusion bodies of inclusion blennorrhea can be demonstrated in fixed tissue of the conjunctiva and of the cervix.

"2. The type of epithelium containing the bodies is the same in the cervix and the conjunctiva.

"3. The inclusions occur almost exclusively in the large polygonal 'wing' cells just above the basal layer.

"4. Hyperplasia, hypertrophy, and desquamation of the epithelium are the predominant histological changes in the virus-infected tissues.

"5. The subepithelial infiltrate of inflammatory cells is nonspecific.

"6. Disintegration of follicles and scarring do not occur."

REESE, Philadelphia. [ARCH. OPHTH.]

STUDIES ON INCLUSION BLENNORRHEA. L. A. JULIANELLE, R. W. HARRISON and A. C. LANGE, Am. J. Ophth. **21**:1230 (Nov.) 1938.

This is the third of a series of studies and has to do with experimental considerations of the causes of inclusion blennorrhea. The authors give the following summary and conclusions.

"1. The bacteria cultivable by a variety of methods from inclusion blennorrhea are representative of the flora associated with the normal conjunctiva.

"2. The bacteria so derived are non-pathogenic and they are incapable of inducing experimental inclusion blennorrhea in the monkey.

"3. The infectious agent of inclusion blennorrhea passes through Berkefeld V filters and collodion membranes of 0.6 A. P. D.

"4. Such filtrates are bacteriologically sterile and induce experimental infection.

"5. Attempts to cultivate the infectious agent in tissue cultures were not successful.

"6. Such tissue cultures were not infectious for monkeys and they did not contain inclusions.

"7. The interrelationships of the virus and the inclusion are discussed."

REESE, Philadelphia. [ARCH. OPHTH.]

RETINAL HEMORRHAGES IN ASSOCIATION WITH MENINGEAL HEMORRHAGE OF THE NEWBORN. G. RENARD, Arch. d'opht. **1**:30 (Jan.) 1937.

Retinal hemorrhages are found in about one third to one half of the newborn with pachymeningitis. The author thinks that the hemorrhages are frequently due to a mechanical factor related to increased intracranial pressure. However, early flame-shaped hemorrhages unaccompanied by papilledema must always be looked for, for they have great diagnostic value. They probably indicate a congenital vascular change, perhaps due to hereditary syphilis.

MARLOW, Syracuse, N. Y. [ARCH. OPHTH.]

GENESIS OF CONGENITAL HYDROPS. G. LIEBEGOTT, Beitr. z. path. Anat. u. z. allg. Path. **101**:319, 1938.

In 2 instances of congenital hydrops there was observed, in addition to the usual anatomic changes, pronounced enlargement of the strikingly numerous islets of Langerhans in the pancreas and marked increase in the width of the zona reticularis of the adrenal gland, the cells of which in the sudan preparations were loaded with neutral fat. These changes were accompanied by massive storage of glycogen in the myocardium, which was interpreted as an expression of hyperinsulinism. It is conjectured that the hyperplasia of the islets is related to a disturance of the maternal carbohydrate metabolism, and this conjecture is to be subjected to experimental investigation.

LEBOWICH, Sloversville, N. Y. [ARCH. PATH.]

BIOCHEMICAL STUDIES OF BLOOD AND SPINAL FLUID IN THE NEWBORN. I. OKUDA, J. Orient. Med. **28**:1043 (May) 1938.

Okuda made intensive studies of the spinal fluid in 132 newborn infants. His observations may be summarized as follows: 1. The pressure varied from 10 to 130 mm. of water during the first two weeks of life but became more stable after the third week. 2. The fluid became definitely icteric within eight hours after birth. 3. The xanthochromia suddenly increased in intensity with the development of clinically discernible jaundice, reaching its peak at about one week. 4. The xanthochromia disappeared gradually after eleven days but for the most part required three to four weeks for complete disappearance. 5. The xanthochromia was due to the presence of bilirubin from the blood serum. Albumin also readily passed through the barrier. 6. Red blood cells also were found in the spinal fluid of all these infants.

KATO, Chicago.

Acute Contagious Diseases

AN ATTEMPT TO INCREASE RESISTANCE TO PERTUSSIS IN NEWBORN INFANTS BY IMMUNIZING THEIR MOTHERS DURING PREGNANCY. J. A. LICHTY JR., B. SLAVIN and W. L. BRADFORD, J. Clin. Investigation **17**:613 (Sept.) 1938.

These studies were designed to determine whether immunization of women with pertussis vaccine during pregnancy would lead to an increase of pertussis antibodies—and increased resistance to the disease—in the fetus and the newborn infant. Observations were made on the infants of 28 immunized mothers and 22 nonimmunized mothers. These were compared with previously published observations on infants of 44 mothers, of whom 25 had had pertussis and 19 had not had pertussis. The opsonocytophagic reaction of the blood of the newborn infant for Haemophilus pertussis is significantly influenced by at least three factors: (*a*) the phagocytic capacity of the mother's blood, (*b*) previous pertussis in the mother and (*c*) artificial immunization of the mother with pertussis vaccine during the latter part of pregnancy. Neither the previous disease nor the artificial immunization with a pertussis vaccine during pregnancy exerted any significant influence on the opsonocytophagic reaction of the mother's blood for H. pertussis.

GUEST, Cincinnati.

FUTURE OF CHEMOPROPHYLAXIS AS A MEASURE FOR THE PRACTICAL CONTROL OF POLIOMYELITIS. E. W. SCHULTZ, J. Pediat. **13**:38 (July) 1938.

This paper begins with a brief review of the chemical substances which have been used intranasally in prophylaxis against anterior poliomyelitis. Among the chemicals which have protective qualities, zinc sulfate has been found to be most effective. A 1 per cent solution of this agent thoroughly applied to the olfactory mucosa in monkeys will protect 90 per cent of them a month later against instillations of virus sufficiently heavy to infect 90 to 100 per cent of an approximately equal number of controls. The mode of action of such chemicals is not known, but Schultz believes that they do not destroy the virus but rather that they modify the permeability of the tissue which serves as the portal of entry. It is not clear how the permeability is influenced, but most of the protective chemicals are fairly acid and strong precipitants of protein, although others are alkaline and poor precipitants of protein. As regards the zinc compounds, the protection they afford may depend on some union of the zinc ion with the protoplasm of the olfactory endings, a zinc proteinate being formed which is less permeable to the virus than the unmodified protoplasm. It is also possible that the protection may result from actual destruction of the olfactory dendrites, possibly even of the olfactory cells themselves, and that the susceptibility returns only after these have regenerated. Schultz discusses in detail the question of the portal by which the virus enters the central nervous system. Experimental evidence is in favor of the olfactory nerve as the usual portal of entry. Whether chemicals will protect man has not been proved. The experiments in Alabama in 1936, in which trinitrophenol-alum spray was used, and those in Toronto in 1937, in which zinc sulfate was used, were inconclusive chiefly because of the difficulty of reaching the olfactory area. Proper methods of application are described. Unless anosmia is produced, one cannot be sure the olfactory area has been completely covered. Schultz believes the basis for deciding what interval of time should elapse between treatments must be based on the presence and degree of anosmia. Contraindications to treatment of the olfactory area with zinc sulfate are chiefly headache, which occurs about twenty minutes after application of the chemical and lasts from three to six hours, and the possibility of permanent anosmia. Though Schultz feels that chemical prophylaxis against anterior poliomyelitis is far from ideal and still in the experimental stage, he believes further work and experimentation in this field are necessary, for at present such prophylaxis offers the only promise of a practical solution.

RAUH, Cincinnati.

ACUTE ANTERIOR POLIOMYELITIS FOLLOWING TONSILLECTOMY AND ADENOIDECTOMY, WITH SPECIAL REFERENCE TO THE BULBAR FORM. R. C. ELEY and C. G. FLAKE, J. Pediat. **13**:63 (July) 1938.

The fact that a bulbar form of acute anterior poliomyelitis has been reported as following recent tonsillectomy and adenoidectomy has suggested that this procedure may in some manner influence the entrance of the virus. A review of 418 consecutive patients with acute poliomyelitis admitted to the Infants' Hospital and the Children's hospitals, Boston is presented.

There were 287 patients with spinal poliomyelitis, and in 8 (2.78 per cent) of these the disease occurred within thirty days after the removal of tonsils and adenoids. In only 3 of these did the disease develop within seven to eighteen days after this operative procedure.

Of 131 patients with bulbar poliomyelitis, 17 (12.98 per cent) had this operation performed within twenty days prior to the onset of their illness. In 15 of these 17 patients the disease developed within the usual incubation period (seventeen to eighteen days). Abstracts of these cases are included in the report.

RAUH, Cincinnati.

THERAPY OF CONVALESCENT HUMAN SERUM. F. CLARKE, Nebraska M. J. **24**:55 (Feb.) 1939.

Convalescent pooled serum is used in both the prevention and the treatment of disease. The demand, especially in the sections of denser population, is increasing. Its use against measles is necessary in debilitated children, in children in hospital wards, in children in orphan asylums and in all children under 5 years of age. In the latter the measles death rate is 4 per cent. Convalescent serum immunizes for a short period only, but there is no objection to repeating the dose. To children under 3 years of age 5 cc. is given; to those over 3, 7.5 cc., and to older children, 10 to 15 cc. These doses if given in the catarrhal stage modify the attack, which is the desired goal, since permanent immunity may result from an attack.

In regard to scarlet fever, the incidence has not been great in Nebraska for several years, nor have such severe complications been present as formerly. Of those exposed, even when there has been intimate contact with the disease, only 10 to 25 per cent become ill. Thalheimer has reported that after prompt administration of convalescent serum only 2.8 per cent contracted the disease. The dose of convalescent serum for prophylaxis in infants and young children is 10 cc.; for prophylaxis in older children and adults, it is 20 cc. By this method protection is usually furnished for a period of ten to fourten days. There are no unfavorable reactions. Usually the intramuscular route is used. In the treatment of the disease the use of the serum keeps the attacks mild, and minimizes complications. Physicians who have used the serum in cases of serious illness are enthusiastic concerning its efficacy. Repeated injections may be given every twelve to twenty-four hours. To the patient severely ill intravenous injections may be given, or combined intravenous and intramuscular injections may be the choice.

It is hoped that the use of serum will produce better and more definite results in infantile paralysis. Convalescent whooping cough serum can do no harm in selected cases and is worthy of trial. In Nebraska the securing and distribution of convalescent serum have been in the hands of physicians under the jurisdiction of the state medical society. Centers are established at various points throughout the state.

HAMILTON, Omaha.

MENINGOCOCCAL BROTH CULTURE FILTRATES: FAILURE OF PROTECTION EXPERIMENTS. B. G. MAEGRAITH, Brit. J. Exper. Path. **19**:95, 1938.

The experiments outlined demonstrate that the "antitoxic," antibacterial and normal serums examined have no power of neutralizing the poisonous filtrates of

broth cultures of meningococci. Serums prepared by injecting these filtrates into rabbits and horses have low agglutinating and precipitating properties and are devoid of protective action against the filtrates. These results are in agreement with those obtained by other workers referred to, so that there appears to be no reliable experimental evidence at present in support of the use of such toxic filtrates for the preparation of therapeutic serum.

FROM AUTHOR'S SUMMARY. [ARCH. PATH.]

MENINGOCOCCAL MENINGITIS TREATED WITH PROSEPTASINE AND SOLUSEPTASINE. R. H. HANNAH and F. G. HOBSON, Lancet **2**:937 (Oct. 22) 1938.

Nine patients suffering from meningococcic meningitis were treated with proseptasine (parabenzylaminobenzenesulfonamide) and soluseptasine, a soluble sodium salt derivative (disodium p-(γ-phenylpropylamino)-d-γ-disulfonate), with 2 deaths. In no case was there any considerable amount of diazotizable substance present in the body fluids in the course of the treatment. In no case were there toxic manifestations.

Of the 2 fatal cases, hydrocephalus was responsible for the fatal termination in the first; in the second, the reappearance of meningococci, despite intensive treatment, appeared to be due to release of a localized collection in the posterior fossa.

LANGMANN, New York.

VARICELLA ENCEPHALITIS. H. GRENET and P. ISAAC-GEORGES, Bull. Soc. de pédiat. de Paris **36**:240 (April) 1938.

A girl 8 years old showed signs of involvement of the cerebellum as well as of the posterior parts of the spinal column or the roots. These signs were noticed one year previous to the time of writing, during the child's convalescence from varicella. Her mentality was unaffected. The spinal fluid was normal.

BENJAMIN, Montreal, Canada.

ACUTE ENCEPHALITIS OF WHOOPING COUGH. R. POINSO and P. SIMÉON, Bull. Soc. de pédiat. de Paris **36**:263 (April) 1938.

A girl 5½ years old began to suffer from severe headache, vomiting, convulsions and fever two weeks after onset of pertussis. The throat was inflamed just before the appearance of the cerebral manifestations. There was some weakness of the left upper extremity. The spinal fluid was normal. She recovered and was perfectly normal a month later.

BENJAMIN, Montreal, Canada.

AN EPIDEMIC OF FACIAL PARALYSIS DUE TO POLIOMYELITIS. M. P. KISSEL, Rev. neurol. **69**:725 (June) 1938.

In August and September 1937 there appeared in a village of 1,000 people 13 cases of poliomyelitis. The first 7 victims showed facial paralyses, complicated with paralysis of the sixth nerve in 4. Of the 6 later presenting the disease, 4 showed medullary forms; 3 died from ascending paralysis. Another patient had a fatal bulbar form with facial paralysis, and the last, uncomplicated facial paralysis. All the patients presented an initial infection of the throat. The author considers the throat the locus of entry of the virus.

DAFFINEE, Boston.

MENINGEAL REACTIONS TO SERUM. F. ROCCHI, Policlinico (sez. med.) **45**:187 (April 1) 1938.

Rocchi discusses the significance of the meningeal reactions which follow intraspinal injections of heterologous serum and the danger of the reactions which take place in the course of serotherapy for epidemic cerebrospinal meningitis. He followed the meningeal reactions which took place in the course of intraspinal

injections of heterologous serum in patients who were suffering from poliomyelitis, tetanus and meningococcic meningitis. The meningeal reaction takes place whether or not the meninges are inflamed. The reaction develops within twenty-four hours after the injection, reaches its greatest intensity in two days and diminishes or disappears in a week. Even though further intraspinal injections of serum are given, the reaction disappears. The meningeal reaction may include the appearance of clinical meningeal symptoms in association with changes in the cytologic reactions of the cerebrospinal fluid or with only the latter. The cytologic reaction consists in predominant polynucleosis in the cerebrospinal fluid with a few histiocytes. The clinical symptoms and the colloidal reactions of the cerebrospinal fluid are of meningitic type. Glycorrhachia is normal. General symptoms of serum anaphylaxis may develop in the course of the reaction, but in all his experience Rocchi has never seen meningeal anaphylaxis. He classifies the meningeal reactions to intraspinal serum therapy as immediate (clinical and cytologic) and late (general or focal anaphylactic). He suggests the name "meningosis" for the meningeal serum reactions. The nature of this reaction, whether toxic or anaphylactic or showing aggravation of meningococcic or suppurative meningitis, can be ascertained by the cytologic picture of the cerebrospinal fluid. Polymorphonuclear leukocytes, which are in abundance in the cerebrospinal fluid during the meningeal reaction, are well preserved and stain normally when there is no meningitis. Pus shows in the cerebrospinal fluid with the Cesaris-Demel reaction when there is meningitis. The author concludes that toxic or anaphylactic reactions to serum do not develop as frequently as is believed and that fear of development of the reaction should not be an obstacle in administration of prolonged serum treatment of epidemic cerebrospinal meningitis. EDITOR'S ABSTRACT. [ARCH. NEUROL. & PSYCHIAT.]

EXPERIMENTAL POSTDIPHTHERITIC PARALYSIS AND VITAMIN B_1. P. SCHIAPARELLI, Riv. di clin. pediat. **36**:1089 (Dec.) 1938.

Experimental postdiphtheritic paralysis was produced by injecting intramuscularly into guinea pigs weighing 200 to 300 Gm. 0.05 cc. doses of Ramon's anatoxin. Large doses of vitamin B_1 were not capable of preventing or curing the paralysis.

HIGGINS, Boston.

LABORATORY DIAGNOSIS OF MALIGNANT DIPHTHERITIC LARYNGITIS. R. ETCHELAR and M. JAUREGUY, Arch. de pediat. d. Uruguay **9**:518 (Aug.) 1938.

Etchelar and Jaureguy report that in the contagious disease service of Uruguay diphtheria has increased from 12 per cent in 1925 to 52 per cent in 1937. Deaths in this service due to the disease have also increased from 14 to 50 per cent. between the dates given. Bacteriologic examinations gave positive findings in 40 per cent of the cases. The authors emphasize the clinical rather than the laboratory findings.

SCHLUTZ, Chicago.

THINGS OF PRACTICAL IMPORTANCE IN DIPHTHERIA. K. SRNETZ, Med. Klin. **34**:611 (May 6) 1938.

Srnetz discusses the difficulties in making the diagnosis of diphtheria and the rapidity with which the findings in the throat may change. He advises against too promiscuous use of serum, because of the danger of sensitization. He thinks not more than 20,000 to 30,000 units of antitoxin should be given. Next to serum treatment, prevention and treatment of cardiac damage are most important. Results with vitamin C, strychnine and other agents have been disappointing. He states that active immunization is apparently becoming the best prophylactic measure but that he cannot speak from personal experience.

SIEMSEN, Chicago.

PARA-SHIGA DYSENTERY BACILLUS. M. ALI, J. Egyptian M. A. **21**:650 (Oct.) 1938.

Ali reviews the literature and reports an investigation of a not uncommon bacillus associated with clinical dysentery in Egypt, resembling the para-Shiga group. During 1935 eight strains were collected in cases of acute dysentery. They were given different names and described as gram-negative small rod-shaped bacilli, varying from 1 to 3 microns in length and from 0.2 to 0.5 micron in thickness. They grew well in all culture mediums ranging in reaction from p_H 6.8 to p_H 8. The eight strains fermented dextrose, levulose and galactose with production of acid but not gas; they did not ferment lactose, saccharose, mannitol, dulcitol, xylose, rhamnose, melitose, inulin, dextrin, adonitol, inosite or salicin. They were found to produce specific agglutinins in serum, and cross agglutination tests effected an arrangement of the strains into four types. The antiserums for these four types were tested against eight true Shiga strains, against Bacterium dysenteriae Shmitz strains and Bacillus ceylonensis A, but no agglutination was observed. Absorption tests gave negative results, and no antigenic relationship to Bacterium dysenteriae Flexner or Bacterium dysenteriae Sonne could be found.

MULHERIN, Augusta, Ga.

EXPERIMENTAL STUDIES ON THE TREATMENT OF MALARIAL SPLENOMEGALIES BY THE METHOD OF ASCOLI. I. F. DE MELLO, South African M. J. **12**:834 (Nov. 26) 1938.

De Mello feels that there is no method of treating patients for malarial splenomegaly which gives such constant reduction in the size of the spleen as the method of Ascoli: daily intravenous injection of progressively increasing doses of epinephrine. Detailed observations on 20 patients so treated are given.

GONCE, Madison, Wis.

SOME FACTS ABOUT CONGENITAL MALARIA. J. S. JUNIOR, Pediat. e puericultura **6**:57 (June) 1937.

The important question of congenital malaria is brought out by the author after a review of the native and foreign literature on the subject. It has been his idea to move native as well as outside workers to investigate the subject, which he believes to be of paramount importance in the prophylaxis of this disease and a matter of the public health. He concludes that the possibility of congenital malaria is no longer in question. However, the occurrence is rare and due in most cases to placental lesions occurring during gestation or at the time of birth.

SOTO, Havana, Cuba.

A STERNAL PUNCTURE TECHNIC AND ITS CLINICAL VALUE, WITH ESPECIAL REFERENCE TO ITS USEFULNESS IN THE DIAGNOSIS OF KALA-AZAR. H. L. CHUNG, Chinese M. J. **54**:397 (Nov.) 1938.

There were 2 infants and 2 older children among the 6 persons cited as having been studied by the technic of sternal puncture which Chung reports for its diagnostic value in this disease. Five of the patients yielded Leishman-Donovan bodies in the marrow smear, making possible their correct treatment with neostibosan (the paraaminophenylstibinate of diethylamine). The method is apparently free from danger, contrasting in this respect with splenic puncture. Typical microscopic sections are reproduced, and the history and technic of the procedure are discussed.

NEFF, Kansas City, Mo.

Chronic Infectious Diseases

TUBERCULIN PATCH TESTS IN CHILDREN. F. D. HART, Lancet **2**:609 (Sept. 10) 1938.

The Mantoux test and the Lederle and Copenhagen patch tests were used in testing 536 children. In 436 of these children the Mantoux test was negative; in 100 it was positive. All of the 436 children with a negative Mantoux test had a negative patch test. Of the 100 children with a positive Mantoux test, 97 had a positive patch test. In 95 children both patch tests were positive. One child had a negative Copenhagen test but a positive Lederle test, and another, vice versa.

There is little to choose between the two types of patch test used. The Copenhagen seems a little preferable, as the tuberculin salve is much less expensive and the amount applied can be regulated. LANGMANN, New York.

USELESSNESS OF OSTEOSYNTHESIS IN MOST CASES OF POTT'S DISEASE IN CHILDREN. E. SORREL, Bull. Soc. de pédiat. de Paris **35**:612 (Nov.) 1937.

A boy 4½ years old had Pott's disease. He was treated conservatively in the usual manner for three and a half years. Now at the age of 14 years he shows practically no deformity, and roentgenograms of his spine demonstrate fusion of the second and third lumbar vertebrae, the site of the original disease. Sorrel points out that whereas in the adult the operation for spinal fusion is simple and well borne, it should not be performed in a child except in very rare instances, owing to growth of the spine. BENJAMIN, Montreal, Canada.

ROENTGENOGRAPHIC APPEARANCE OF MILIARY DISTRIBUTION AT THE ONSET OF AMBULATORY PULMONARY TUBERCULOSIS. PIERRE-PAUL LÉVY, CHEVALIER and SCHERMANN, Bull. Soc. de pédiat. de Paris **36**:175 (March) 1938.

A 9 year old boy had a positive tuberculin test and mild symptoms of tuberculosis. Contrasting with his general condition, a roentgenogram of his chest showed bilateral diffuse miliary infiltration. Examination of the stools and tracheal mucus for tubercle bacilli gave negative results. He was observed for a month and was then sent to the mountains. Some speculative remarks are made as to what the subsequent course of his illness might be. BENJAMIN, Montreal, Canada.

SOME METHODS FOR THE DIAGNOSIS OF TUBERCULOUS MENINGITIS. M. MANICATIDE, Méd. inf. **1**:6 (Jan.) 1939.

Among the methods proposed for the diagnosis of tuberculous meningitis, the surest still remains a lumbar puncture with the spinal fluid showing acid-fast bacilli in the clot which forms near the surface of the fluid—a method which the author has insisted on for forty years and which has always shown the bacillus of Koch in tuberculous meningitis. FROM THE AUTHOR'S SUMMARY.

CONGENITAL ORIGIN OF MILIARY TUBERCULOSIS. T. GANE, I. TOMA and S. PETRESCO, Méd. inf. **1**:9 (Jan.) 1939.

After reviewing different opinions as to congenital tuberculosis, the authors report in detail on a child born at term of a tuberculous mother. The weight at birth was 1,980 Gm. Although the child was separated from the mother within the first hour of life, it presented at the age of 23 days the first symptoms of pulmonary disease and marked general symptoms (stationary weight, pallor, cough, dyspnea). A Pirquet test on the twenty-eighth day was negative. The child died

at the age of 1 month and 23 days with symptoms of asphyxia. The autopsy showed generalized tuberculosis, miliary in type, which in the lungs showed also a nodular development. Microscopic examination of sections from different organs showed exudative lesions and in the liver exudative and proliferative nodular lesions. There was, therefore, general miliary tuberculosis with localizations chiefly in the lung, a form frequently described by authors in infants who are considered to have lesions of congenital origin. An infection taking place a few hours after birth is scarcely probable. Such cases are rarely cited in the literature.

FROM THE AUTHOR'S SUMMARY.

TUBERCULOUS POLYSEROSITIS. A. SEGERS and A. RUSSO, Arch. argent. de pediat. **2**:246 (Sept.) 1938.

Segers and Russo describe exudative polyserositis of a tuberculous nature in a 12 year old girl. The diagnosis had to be made by exclusion as the disease simulated septicemia, typhoid and brucelliasis. Patients with this condition in a mild form may recover, but recurrences and miliary spread are usual. To the time of writing the course in the case described has been favorable, but the prognosis is uncertain.

SCHLUTZ, Chicago.

THE COLLOIDAL CARBON REACTION OF THE CEREBROSPINAL FLUID. A. ORTEGA IRAGORRI, Arch. de neurol. y psiquiat. de Mexico **1**:329, 1938.

Iragorri describes a modification of the technic used by Schube and Harms. Seven tubes are used, each containing constant amounts of distilled water, oxalic acid and diluted india ink. To six tubes spinal fluid is added in descending concentrations; the seventh is a control. The tubes are centrifuged for from ten to fifteen minutes at a speed of from 3,000 to 4,000 revolutions per minute, and may then be read directly. In the positive tubes the degree of flocculation is graded on a scale of from 1 to 4, 4 representing complete flocculation. Frequently the first tube shows less flocculation than the second or third.

Of 850 cases in which examination was made, a positive reaction was elicited in only 1 case—a case of syphilis. The test appears to be specific for syphilis and to be especially useful in doubtful cases.

KING, Princeton, N. J. [ARCH. NEUROL. & PSYCHIAT.]

YOSHIDA'S TEST IN REGARD TO ACTIVE TUBERCULOSIS. C. MARQUES DIAS, Arch. de pediat. **10**:553 (Aug.) 1938.

The subject of active and inactive tuberculosis is brought out with the remark that tuberculosis is to be considered as the response of the patient's defenses in the face of the tubercle bacillus. This response can be judged by clinical as well as by laboratory methods, the author offering an analysis of only the most important laboratory methods of investigation. The author believes Yoshida's test may be of the greatest importance. This test is based on the production of leukopenia by an injection of the so-called A-O vaccine, which is prepared from human strains of the tubercle bacillus by the special technic recommended by the Japanese authors. The author states that a patient with active tuberculosis would always show leukopenia. The test is reported as slightly positive, positive and strongly positive according to the degree of leukopenia attained after the subcutaneous injection of 1 cc. of the vaccine.

There is no mention as to whether or not the test might be positive in such diseases as syphilis, rheumatic fever and leprosy.

SOTO, Habana, Cuba.

CARE OF TOMORROW. B. KRAKOWSKI, Zycie Mlodych **7**:123 (May) 1938.

Krakowski discusses the potential danger of tuberculosis to children in Poland. Although much is done in Poland along the line of prophylaxis and about 400,000 children profit by it, tuberculosis is on the increase. In conclusion he calls on every agency in Poland to fight tuberculosis.

KRUPINSKI, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

SCHÜLLER-CHRISTIAN'S DISEASE. E. J. WYNKOOP and L. HADLEY, Arch. Pediat. **55**:417 (July) 1938.

The authors have observed Schüller-Christian disease in a girl for a period of two years. She was first seen at the age of 2 years and 9 months. Improvement has occurred following small doses of roentgen radiation.

ORR, Buffalo.

SEVERE HEMOLYTIC ANEMIA DUE TO SULFANILAMIDE. P. ROSENBLUM and A. H. ROSENBLUM, Arch. Pediat. **55**:511 (Aug.) 1938.

A boy aged 10 years, weighing 101 pounds (45.8 Kg.), was being treated with sulfanilamide. The dosage was 5 grains (0.3 Gm.) every four hours. Thirty grains had been given when the child showed marked pallor and icterus and appeared very toxic, although his temperature was normal. Studies of the blood revealed definite evidence of hemolytic anemia. Recovery was prompt after two blood transfusions.

ORR, Buffalo.

A SIMPLE METHOD FOR ESTIMATION OF TOTAL PROTEIN CONTENT OF PLASMA AND SERUM: II. ESTIMATION OF THE TOTAL PROTEIN CONTENT OF HUMAN PLASMA AND SERUM BY USE OF THE FALLING DROP METHOD. B. M. KAGAN, J. Clin. Investigation **17**:373 (July) 1938.

1. A simple, rapid and easy method for the determination of specific gravity is based on Stokes' law for the velocity of falling bodies. A drop of serum, accurately measured, is delivered into a column of immiscible fluid, and the time required for the drop to fall through a distance of 1 cm. is determined with a stopwatch. A mixture of synthetic methyl salicylate and heavy mineral oil is used as the immiscible fluid, adjusted to a specific gravity of 1.0130 at 25 C. The method gives the specific gravity of serum or plasma with a maximum difference from that determined by a 2 cc. pyknometer of 4×10^{-4} and has a range of 1.0150 to 1.0370.

2. Because of the linear relationship which exists between the specific gravity and the protein content of blood serum, the falling drop method can be used for the determination of protein concentration of the serum. The determination, made with small quantities of blood and quickly, has an accuracy which exceeds clinical requirements and is about twice as accurate as the refractometric method.

GUEST, Cincinnati.

BLOOD IODINE IN LEUKEMIA. K. B. TURNER, K. R. MCALPIN and A. DELAMATER, Proc. Soc. Exper. Biol. & Med. **39**:55 (Oct.) 1938.

The blood iodine (determined by the method of Trevorrow and Fashena [*J. Biol. Chem.* **110**:29, 1935]) was normal or high in 12 cases of lymphatic leukemia (average, 10.24 per hundred cubic centimeters), whereas in 5 cases of myeloid leukemia it tended to be low (average, 3.34). The normal range is 3.5 to 6.04. In 2 cases of lymphosarcoma the blood iodine was found to be high; in 2 cases of Hodgkin's disease it was slightly elevated, and in 2 others it was normal.

HANSEN, Minneapolis.

PAROXYSMAL TACHYCARDIA. P. LAURENTIUS, Monatschr. f. Kinderh. **77**:30 (Jan.) 1939.

Laurentius briefly reports 3 cases of paroxysmal tachycardia with the electrocardiographic findings.

GERSTLEY, Chicago.

VEGETATIVE REGULATION OF THE RED BLOOD CELLS IN ANEMIA. H. KINKEL and G. KINKEL-DIERCKS, Monatschr. f. Kinderh. **77**:153 (Feb.) 1939.

These writers report the influence on the number of red cells in the blood of drugs stimulating the sympathetic and parasympathetic nervous system. They attempt to classify their cases into two groups: those of hypochromic and those of hyperchromic anemia.

Administered to patients with hyperchromic anemia, pilocarpine, a stimulant to the parasympathetic nerves, causes an increase in the numbers of reticulocytes after about thirty minutes. Atropine, a drug that paralyzes the parasympathetic nerves, causes a diminution in the number of reticulocytes. Epinephrine, a stimulant to the sympathetic nerves, causes a diminution in the number of reticulocytes. Ergotamine, a drug that paralyzes the sympathetic nerves, causes an increase in the number of reticulocytes.

The article is very involved.

GERSTLEY, Chicago.

THE BOTTNER AND THE KAUFFMANN METHOD OF DETERMINING HEART FUNCTION. K. KUMMER, Monatschr. f. Kinderh. **77**:203 (Feb.) 1939.

These two procedures are based on the same fundamental principle, namely, that of giving a child a large quantity of fluid in the morning and measuring the rate of excretion. With the first method 1,000 cc. is given in one dose; with the other 100 cc. is given every hour for six doses. Kummer finds the results so variable that he believes neither is adapted to testing cardiac function.

GERSTLEY, Chicago.

MYELOSARCOMA SIMULATING CHLOROMA. C. DE LANGE, Acta pædiat. **23**:183, 1938.

De Lange reports in considerable detail the clinical course and pathologic observations in the case of a 1 year old infant whose fatal illness exhibited a puzzling but suggestive combination of features usually regarded as characteristic of myeloid leukemia, on one hand, and of chloroma on the other. The condition is regarded as blastomatosis of the hemopoietic apparatus. Looked at from this point of view, the case supplies another argument for the neoplastic nature of leukemia.

McCUNE, New York.

FOUR CASES OF CONGENITAL CARDIAC DISEASE. E. MANNHEIMER and P. J. NORDENFELT, Acta pædiat. **23**:200, 1938.

The anomalies described are: cor biloculare with persistent truncus arteriosus; complete transposition with defect of the interventricular septum; complete transposition without defect of the interventricular septum; stenosis of the aortic valve. The cases are reported in detail; roentgenographic and electrocardiographic data are presented. The anomalies described are all of rare type. The clinical differential diagnosis presents well nigh insuperable difficulties.

McCUNE, New York.

ALEUKEMIC MYELOSIS WITH SKELETAL CHANGES IN A SEVEN YEAR OLD BOY. O. LÖVGREN and P. B. EDÉN, Acta pædiat. **23**:222, 1938.

In this case of aleukemic myeloid leukemia in a 7 year old boy marked destructive changes in the skeleton were demonstrated by the roentgenograms. The serum calcium was increased to between 11.4 and 15.2 mg. per hundred cubic centimeters,

and the serum inorganic phosphorus to 6.5 mg. per hundred cubic centimeters. Leukemia was suggested by splenomegaly and leukopenia and was diagnosed by sternal puncture; the diagnosis was confirmed at autopsy. As a matter of general interest, it is a pity that the parathyroid glands were not examined. Cases of this sort are rare but not unique as the authors assert (see Duken, J.: *Ztschr. f. Kinderh.* **46**:114, 1928). The manifestations referable to the skeleton may give rise to confusion with multiple myeloma, xanthomatosis, sarcomatosis of bone, syphilis and sepsis. The differential diagnosis is more promptly made if this possibility is kept in mind.

McCune, New York.

Diseases of Nose, Throat and Ear

Pediatric Treatment of Otologic Sepsis, Including Meningitis. P. L. Aries, Illinois M. J. **75**:131 (Feb.) 1939.

This is a rather detailed discussion of the various methods of treatment which may be indicated in cases of otologic sepsis and associated conditions, including meningitis.

Barbour, Peoria, Ill.

Nasal Septum Surgery in Children. M. H. Cottle, Illinois M. J. **75**:161 (Feb.) 1939.

Following a discussion of the histologic aspects, causes, symptoms and treatment of deviations of the nasal septum, Cottle concludes that frequently nasal obstruction and chronic discharge are the result of septal deviation, that often nonsurgical treatment is needed and is adequate, that occasionally surgical measures are indicated and that the type of operation which is appropriate to an adult is unnecessarily radical for a child in all but the very rare instances of extreme deformity.

Barbour, Peoria, Ill.

Biologic Significance of the Tonsils and Adenoids and Other External Lymphoid Masses. P. W. Leathart, Brit. M. J. **2**:835 (Oct. 22) 1938.

This is a discussion along the lines indicated in the title. In general, it is a plea for conservatism in respect to the tonsils and adenoids. Leathart concludes:

"1. That the function of an external lymphoid mass is to collect micro-organisms from food or air and to grow those to which an immunity is needed.

"2. That the condition 'enlarged tonsils' alone is definitely an indication against their removal.

"3. That the adenoid facies is more commonly caused by catarrhal sinusitis than by an adenoid mass.

"4. That catarrhal sinusitis can be treated successfully in a large number of cases without operation, by giving a 'nasal aperient.' [This term refers to a relatively prolonged administration of potassium iodide. Abstractor.]

"5. That tonsils and adenoids at the present time are removed too frequently and without due consideration of their important biological function.

"6. That many cases of rheumatic fever and acute nephritis that are going downhill can be cured or greatly benefited by removal of the 'carrier organ'."

Royster, University, Va.

Sulphonamide in the Treatment of Acute Mastoiditis. V. G. Horan and S. G. French, Brit. M. J. **2**:942 (Nov. 5) 1938.

These observations were made at the Royal Naval Hospital, Chatham, England, and presumably were made on adults. However, the work probably applies equally to children, although this is not definitely determined. The authors point out that there is a seasonal variation in mastoid complications of middle ear disease. The surgeon of today is apt to adopt an expectant line of treatment rather than the radical one. It is important that administration of sulfanilamide be practiced early rather than late. On account of this practice it may be that an error in estimating

results arises in that many who were expected to have mastoid involvement might not have reached that stage in any event. The argument and statement of experience are conservative. The conclusions are that in spite of the possible sources of error in the figures published in the report the incidence of acute mastoiditis in the Royal Naval Hospital, Chatham, has been notably reduced, and since the only difference in the treatment of acute disease of the ear has been the introduction of routine administration of sulfanilamide on admission, it is reasonable to suppose that the aforementioned drop in mastoiditis is due to the use of the drug. Therefore the sulfanilamide group of drugs have a real place in the treatment of acute suppurative otitis media.

ROYSTER, University, Va.

HAEMORRHAGE FOLLOWING TONSILLECTOMY. D. W. ASHCRAFT, Brit. M. J. **2**:1078 (Nov. 26) 1938.

The subject is treated under the three following headings:

I. Factors influencing the occurrence of hemorrhage following tonsillectomy: (*a*) preoperative; (*b*) operative; (*c*) postoperative.

II. Types of postoperative hemorrhage.

III. The management of hemorrhage following tonsillectomy.

The preoperative factors influencing the occurrence of hemorrhage following tonsillectomy are: 1. Severe tonsillitis or peritonsillar abscess. Recent infections increase the risk of hemorrhage. Therefore, following one of these conditions, a few weeks should elapse before operation.

2. Infections of the nose or nasal accessory sinuses. Acute sinusitis is a contraindication to immediate performance of the operation; likewise, the common cold. Chronic sinusitis should not be overlooked. Treatment for this condition should be instituted before tonsillectomy is considered.

3. Bleeding. If there is a history of susceptibility to prolonged bleeding, an investigation should be made before operation. The common coagulation time is four to seven minutes; the bleeding time one to four minutes. If they are prolonged, calcium and alkalis should be given or a blood transfusion performed. If bleeding cannot be controlled, tonsillectomy, unless absolutely necessary, should not be considered.

4. Menstruation. The objection to an operation in this period is based on psychologic considerations rather than on fear of hemorrhage.

5. Jaundice. Tonsillectomy is contraindicated in the presence of jaundice.

6. Anemia. Tonsillectomy should not be performed unless preliminary treatment is given; even a blood transfusion may be advisable.

7. Type of patient. This concerns the adult rather than the child.

The operative factors are now taken up. The type of operation is discussed. Chloroform anesthesia or deep anesthesia induced by any other agent results in a fall of blood pressure. Therefore, when the blood pressure regains its normal level, hemorrage may occur. Clot formation is liable to be imperfect in the larger veins in the bed of the tonsillar fossa. Especially is this likely to be so when there has been a complete division of a large longitudinal vein. The bleeding point must be searched for and tied. The maintenance of a clear airway is very important following tonsillectomy. Hence it is important that an artificial airway be inserted in the mouth after all the blood clot has been removed. One must be certain that all ligatures are securely tied. Vasoconstrictors are not to be recommended for use at the time of operation because of the subsequent reaction of capillary ooze.

The postoperative factors are considered as follows. All conditions tending to cause congestion are to be avoided after the operation. In bed, the patient should be in the "lateral" position. The artificial airway should be removed when the cough reflex has returned. Restlessness after operation calls for a sedative. Children should have an enema containing bromides. No hot fluids are to be permitted during the first twenty-four hours. Cold fluids or semisolid food are given during

the first day. The patient should be allowed out of bed for the first time on the evening of the third day following operation. No hot baths are allowed in the first ten days after the operation. For a week after leaving the hospital there must be avoidance of all strenuous exercise. A mixture containing potassium chlorate, sodium salicylate and sodium bicarbonate should be given three times daily throughout convalescence.

The types of hemorrhage are: (1) reactionary hemorrhage occurring within the first twenty-four hours after operation, (2) hemorrhage during convalescence and (3) true secondary hemorrhage. The management of these types is as follows: For the reactionary ooze the author prefers morphine in the case of adults and children over 10 years but not in the case of children under this age. He prefers bromide and chloral hydrate for children under 10 years. The material for the treatment of reactionary hemorrhage is too extensive to abstract. Hemorrhage during convalescence occurs usually on the fifth night following operation and is due to factors already enumerated. As a rule, it is not severe, and for this the author uses a gargle of weak hydrogen peroxide. Clot should not be removed as it may remove itself following the act of gargling. True secondary hemorrhage is much more serious than the other type. It is also rare. Control of such hemorrhage is difficult in many cases, as it is seldom possible to clamp and ligate a single bleeding point. Recourse to suturing the faucial pillars may be necessary. Other measures which have been recommended are of doubtful value in the author's experience.

ROYSTER, University, Va.

Diseases of Lungs, Pleura and Mediastinum

SERUM THERAPY IN LOBAR PNEUMONIA. W. H. KELLEY, J. South Carolina M. A. **34**:279 (Nov.) 1938.

The mortality from pneumonia has been reduced sharply by the use of specific serum therapy. The methods of typing pneumonia are discussed. The sooner the serum is given after the diagnosis is made, especially if given within forty-eight hours, the better the results. The cost of the serum is still too high for the average patient. Serum is not generally used for infants, and the outlook for children except those with XIV infection is so bright until the age of 12 that the specific therapy is not ordinarily employed for them. One must always be careful in administering this serum to hyperallergic persons.

WESTON, Columbia, S. C.

THE CAUSATIVE ORGANISMS OF BRONCHOPNEUMONIA IN INFANTS IN EGYPT. A. K. ABDEL-KHALIK, A. M. ASKAR and MOHAMED ALI, Arch. Dis. Childhood **13**:333 (Dec.) 1938.

Puncture of a lung has been shown to be the best way to isolate the causative organism in bronchopneumonia in early life. The technic of this type of puncture is described in detail and its safety proved. During the winters of 1932-1936 lungs were punctured in 233 patients with bronchopneumonia, and the material obtained was cultured on blood agar and broth. Of the 182 patients whose cultures were positive, 106 (58.3 per cent) showed one organism, 58 (31.9 per cent) showed two organisms, 15 (8.2 per cent) showed three organisms and 3 (1.6 per cent) showed four organisms. The commonest organism found was Bacillus influenzae (42.3 per cent); then Staphylococcus (36.8 per cent), Streptococcus (23.1 per cent), Pneumococcus (17.6 per cent) and Micrococcus catarrhalis (16.5 per cent). Of the 27 cases in which pneumococci were typed, 4 cases (14.8 per cent) showed type I, 7 cases (26 per cent) type II, 3 cases (11.1 per cent) type III and 13 cases (48.1 per cent) type IV.

KELLY, Milwaukee.

BRONCHIECTASIS: A FATAL DISEASE. H. A. COOKSON and G. A. MASON, Edinburgh M. J. **45**:844 (Dec.) 1938.

The incidence of bronchiectasis is not known. The disease seems to be increasing, but this may be due to the use of better diagnostic measures. There is sometimes confusion as to the identity of chronic bronchitis and bronchiectasis.

Cookson and Mason include among the cases cited only 2 involving children. The children were aged 7 and approximately 3 years. The younger child came to autopsy. A photograph of a cross section shows extensive bronchiectasis. There were also pneumonic consolidation and hilar adenopathies. Among the conclusions is the following: As the condition often begins in childhood, the disease might be eradicated if a complete investigation and proper treatment were employed at that time of life.

NEFF, Kansas City, Mo.

AIR CYSTS OF THE LEFT LUNG WITH DISPLACEMENT OF THE HEART TO THE RIGHT IN AN INFANT. R. POINSO, A. ASTIER and VIENS, Bull. Soc. de pédiat. de Paris **36**:258 (April) 1938.

A 5 week old boy had marked dyspnea and intermittent cyanosis. The heart beat was irregular, and the liver was enlarged. Breath sounds were absent over the anterior and lateral aspects of the left hemithorax, which was resonant. A roentgenogram of the chest showed the heart to be displaced into the right half; the upper lobe of the right lung was atelectatic, and the base of the left lung was unusually transparent, with only a few denser annular lines at its medial part. As a last resort, a needle was inserted into the left side of the chest, from which air under pressure was obtained. This procedure was repeated but gave only slight transient relief to the infant, who died at the age of 47 days. No autopsy is mentioned.

BENJAMIN, Montreal, Canada.

INTERSTITIAL EMPHYSEMA IN AN ASTHMATIC PATIENT. F. SCHWEIZER and O. H. SENET, Arch. de pediat. d. Uruguay **9**:573 (Sept.) 1938.

Schweizer and Senet present a case of asthma and tuberculosis in a 3 year old girl. She had emphysema in the right thorax due to air passing through a pleural adhesion. The emphysema extended from the axilla to the pubis and was reabsorbed in fifteen days.

SCHLUTZ, Chicago.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

PROLAPSUS INTUSSUSCEPTI. I. LE BELL, Arch. Pediat. **55**:475 (Aug.) 1938.

A case is reported.

ORR, Buffalo.

SURGICAL TREATMENT OF CONGENITAL MEGACOLON. J. BROWDER and C. JETT-JACKSON, Brooklyn Hosp. J. **1**:5 (Jan.) 1939.

A review of the literature pertaining to the sympathetic and parasympathetic nerve supply to the colon and anal sphincters indicates that present knowledge concerning the form and function of these nerves in man is deficient.

The improved colonic function produced by partial denervation of the involved portion of the large intestine in Hirschsprung's disease has established this surgical practice as the best form of therapy.

The development of the surgical procedures commonly employed in the treatment of this disorder has been traced and the important advances relative thereto given appropriate consideration.

Seven cases in which congenital megacolon was treated by surgical interruption of a part of the sympathetic nerve supply to the colon and anal sphincters have been studied. The salient clinical features have been recorded in a chart. Two cases in the series, used as illustrative cases, have been reported in some detail.

Comparative roentgen studies indicate that although there is improvement in colonic function following sympathectomy and/or sympathetic ganglionectomy the size of the intestinal lumen is not necessarily decreased.

FROM AUTHORS' SUMMARY.

INTUSSUSCEPTION. P. ROSENBLUM, Illinois M. J. **74**:309 (Oct.) 1938.

Rosenblum summarizes his discussion of intussusception as follows: Intussusception is essentially a pediatric disease. The earlier the diagnosis, the better the prognosis will be. In the acute variety the onset is sudden. The patient has intermittent colicky pain, vomiting, a palpable mass and blood in the stool. The incidence is greatest in males (2:1). Seventy-five per cent of the patients are under 1 year of age. Ten per cent of the patients show no blood in the stools. Usually a mass can be felt. If necessary, the physician should give an anesthetic or an analgesic. Roentgen examination is very helpful, especially in dealing with the subacute and chronic types. Postoperative care, such as supplying fluids, is of great importance.

BARBOUR, Peoria, Ill.

LYE POISONING AND STRICTURE OF THE ESOPHAGUS. J. M. MARTIN and J. M. ARENA, South. M. J. **32**:286 (March) 1939.

Martin and Arena describe 48 cases of corrosive stricture of the esophagus due to ingestion of various preparations of sodium hydroxide.

After swallowing of a caustic alkali the patient should be given the proper antidote by mouth. Emetics and gastric lavage should be discouraged. After the fourth day, when edema and esophagitis have subsided, the method outlined by Bokay for the prevention of stricture should be given a fair trial.

In over 50 per cent of the patients who had not had the Bokay treatment sufficient obstructive symptoms developed thirty-two days after the ingestion of the caustic to warrant hospitalization. In the other patients signs of obstruction developed later.

After stenosis of the esophagus has occurred, the pediatrician and the otolaryngologist should combine their efforts and use measures which are appropriate for the individual patient.

SCHLUTZ, Chicago.

FUSOSPIRILLAR STOMATITIS. J. P. PAQUETTE, Union méd. du Canada **67**:357 (March) 1938.

Paquette presents 11 cases in which he treated Vincent's angina with various forms of arsenic, locally and parenterally. Improvement was rapid in all the cases.

DAFFINEE, Boston.

HERNIA IN INFANCY. C. T. THOMPSON, West Virginia M. J. **35**:158 (April) 1939.

Hernia is frequent in children. It is generally congenital. It is a developmental defect, comparable to harelip or cleft palate. There is a hereditary tendency. It is amenable to treatment, either mechanical or surgical. Actual herniation is produced by increased intra-abdominal tension, such as coughing, crying or straining at stool. Strangulation may occur. Treatment consists in relieving causes of intra-abdominal tension and properly applying adhesive straps for periods of six to ten months. As to surgical repair, operation is suited to the case. The use of trusses is illogical. Illustrative case histories are given.

SHAWKEY, Charleston, W. Va.

CONGENITAL PYLORIC STENOSIS WITH CARDIO-STENOSIS IN A CHILD AGED FOUR DAYS. B. SCHLESSINGER, Proc. Roy. Soc. Med. **32**:137 (Jan.) 1939.

The delivery was normal, but the baby vomited all gastric contents from the time of birth and appeared to be in great discomfort after his feedings, which seemed to embarrass respirations. After feeding, no peristalsis was visible. A

tumor was not felt. The stomach was washed out, but the baby continued to vomit. The washing out caused some distress and cyanosis. Pneumonia developed. Roentgenograms of a barium sulfate meal were taken and showed marked cardiospasm, great enlargement of the stomach, much residue after nineteen hours and some after thirty-six hours. The baby died, and postmortem examination revealed a much dilated esophagus with thickened walls and definite thickening at the cardiac orifice. The stomach was also dilated, with a thin wall and muscular hypertrophy of the pylorus. The lungs showed widespread bronchopneumonia.

WILLIAMSON, New Orleans.

DUODENAL STENOSIS IN A NEWBORN INFANT. H. G. HUBER, Kinderärztl. Praxis **9**:415 (Oct.) 1938.

At the age of 3 days an infant was seized with projectile vomiting. The vomitus contained bile. In the four days following, there was a loss in weight of 1 pound (0.5 Kg.). On account of the infant's poor general condition, the surgeon refused to operate. A quick recovery was attained by the use of infusions, stomach lavage and atropine. The literature on functional duodenal spasm in the newborn is briefly reviewed.

HEYMANN, Cleveland.

Nervous Diseases

OCULAR SIGNS OF INTRACRANIAL DISEASE IN CHILDREN AND JUVENILES. E. W. NEWMAN, Am. J. Ophth. **21**:286 (March) 1938.

Newman studied 42 cases of intracranial disease in children and juvenile patients and presents the following summary:

"1. Changes in the optic discs were found in 95.2 per cent of cases; this fact emphasizes the importance of an ophthalmoscopic examination in all children with findings which might in any way lead to a suspicion of intracranial disease.

"2. Loss of vision was registered as a complaint in only 23.8 per cent of the cases in spite of the fact that 95.2 per cent of the cases presented abnormalities of the optic discs. This is due to the fact that children do not appreciate failure of vision so readily as do adults, and that choked discs do not affect the vision for some time.

"3. Nystagmus was present in 21.4 per cent of the patients, all of whom had tumor of the brain and, with one exception, occurred with a tumor of the cerebellum.

"4. Of the total number of patients in this series, 55 per cent had brain tumors. Histological verification was possible in all except two cases, in which the cerebellar lesion was seen at the time of decompression. The optic discs were normal in only one case, a subtentorial lesion.

"5. A case of high-cervical-cord tumor associated with bilateral choked discs is reported, and a short review of the literature pertaining thereto is cited.

"6. This study emphasizes the extreme importance of a thorough ocular examination. The omission of a fundus examination is often the reason for failure in reaching a correct diagnosis; this is especially true in the case of children, in whom other examinations may be difficult."

REESE, Philadelphia. [ARCH. OPHTH.]

PATHOGENESIS OF SYRINGOMYELIA: CASE ILLUSTRATING THE PROCESS OF CAVITY FORMATION FROM EMBRYONIC CELL RESTS. K. TAMAKI and A. J. LUBIN, Arch. Neurol. & Psychiat. **40**:748 (Oct.) 1938.

After pathologic study of a case of syringomyelia the authors conclude that the condition "is a developmental anomaly caused by imperfect formation of the central canal by primitive medullary epithelium. Resultant cell rests later undergo gliosis."

BEVERLY, Chicago.

CONGENITAL MORPHOLOGIC ABNORMALITIES OF THE BRAIN IN A CASE OF ABORTIVE TUBEROUS SCLEROSIS: FUNCTIONAL IMPLICATIONS AND BEARING ON PATHOGENESIS OF SO-CALLED GENUINE EPILEPSY. P. I. YAKOVLEV, Arch. Neurol. & Psychiat. **41**:119 (Jan.) 1939.

Yakovlev reports in detail the case of a 13 year old girl who entered an institution because of epilepsy and mental deterioration. She died two years later. A pathologic study revealed gross and microscopic changes in the brain typical of tuberous sclerosis, a condition which was not suspected before death. From these findings, the author theorizes on the possibility that idiopathic epilepsy is a congenital functional and therefore structural malformation of a specific reflex mechanism in the brain.

BEVERLY, Chicago.

HUMAN ENCEPHALITIS: EIGHT FATAL CASES, WITH FOUR DUE TO THE VIRUS OF EQUINE ENCEPHALOMYELITIS. C. WESSELHOEFT, E. C. SMITH and C. F. BRANCH, J. A. M. A. **111**:1735 (Nov. 5) 1938.

During an epidemic of 200 cases of equine encephalomyelitis 8 fatal cases of encephalitis occurred in man, 7 in infants, and in 4 of these the virus of the eastern strain of equine encephalomyelitis was found. The infants showed an acute and fulminating illness with restlessness, irritability, anorexia, drowsiness, fever, vomiting, coma, twitching, convulsions, rigidity of the neck, neurologic changes and an increase in the number of cells in the spinal fluid.

Three of these infants had pertussis and in 2 of these the presence of the equine virus was demonstrated. The pathologic appearance of the central nervous system was distinctive with intense congestion, perivascular infiltration, and degeneration of the nerve cells.

HEERSMA, Kalamazoo, Mich.

CHOREA AND ATHETOSIS IN CHILDHOOD. J. SHAFAR, Brit. J. Child. Dis. **35**:259 (Oct.-Dec.) 1938.

Athetoid movements are not unlike choreiform movements slowed down, and according to Shafar the mechanism of their production is probably similar if not identical in origin. The most significant difference between the two seems to be in muscular tone. In chorea the muscles are hypotonic whereas in athetosis they are hypertonic.

The causes of these disturbances of motility are obscure. The disturbances may result from "release" of some system from higher control, or they may result from the perverted activity of a damaged structure. The pathologic changes have been so diffuse that it has not been possible to name any one anatomic site as that of the essential lesion.

In addition to Sydenham's chorea, Shafar takes up in turn the following: the choreiform movements related to epidemic encephalitis; the cerebral sclerosis of Pelizaeus-Merzbacher disease; Friedreich's ataxia; the choreoathetosis sometimes seen in cases of kernicterus. He considers also congenital choreoathetosis (Vogt's syndrome, or status marmoratus), thought to be due to agenesis of some portion of the central nervous system.

LANGMANN, New York.

MENINGO-ENCEPHALITIS DUE TO CRYPTOCOCCUS MENINGITIDIS (TORULA HISTOLYTICA). J. G. GREENFIELD, J. P. MARTIN and M. T. MOORE, Lancet **2**:1154 (Nov. 19) 1938.

A fatal case of meningoencephalitis due to Cryptococcus meningitidis is described. The organism may have gained entry through an abrasion of the skin of the hand. The diagnosis here and in other recorded cases was not made until after death.

LANGMANN, New York.

HISTOLOGIC EXAMINATION OF THE HYPOTHALAMUS IN ORDINARY OBESITY, IN MORGAGNI'S AND GÜNTHER'S SYNDROMES AND IN MORBUS CUSHING. W. RITTER, Frankfurt. Ztschr. f. Path. **52**:149 (May 18) 1938.

Ritter made microscopic studies of the hypothalamus and the adjoining regions in four types of obesity: so-called constitutional obesity, Morgagni's syndrome (endocraniosis hyperostotica with obesity and virilism), Günther's syndrome (cerebral polyglobulism) and Cushing's disease. The aim was to detect possible morphologic changes. Whereas the results of this examination were entirely without significance, the hypophysis showed severe basophilism in all four types of obesity. Moreover, examination of the adrenals disclosed lipoid hyperplasia of the adrenal cortex. The basophilism of the hypophysis is probably not the cause of the obesity but represents rather a compensatory process elicited by the disturbance in the equilibrium of the endocrine organs involved in the fat metabolism. In this connection, the author points out that the formation of adenomas in the parathyroids in a number of diseases of the bone (rickets, osteitis deformans, osteomalacia) is likewise regarded as a secondary process, an adjustment to the changed conditions in the calcium metabolism. The changes which were observed in the anterior lobe of the hypophysis in all four types of obesity corroborate the relations between the basophil cells of the hypophysis and fat metabolism, to which attention had been called by Kraus.

EDITOR'S ABSTRACT. [ARCH. NEUROL. & PSYCHIAT.]

A CASE OF HYPOPLASIA OF THE CEREBRAL MOTOR NUCLEI OR NERVES, COMBINED WITH CLINOCEPHALY. P. J. WAARDENBURG, Maandschr. v. kindergeneesk. **7**:391 (July) 1938.

A boy presents probable hypoplasia of cerebral motor nuclei or nerves, in connection with cryptorchidism, partial debility and clinocephaly. The motor disturbances are ptosis, ophthalmoplegia and paralysis of the facial nerve, probably also paresis of the mandibular nerve. The boy is now 10 years old. The report is illustrated with many roentgenograms and figures.

VAN CREVELD, Amsterdam, Netherlands.

THERAPY OF ENCEPHALITIS AND RELATED NEUROTROPIC INFECTIONS OF THE NERVOUS SYSTEM. W. M. VAN DER SCHEER and R. ZIJLSTRA, Nederl. tijdschr. v. geneesk. **82**:4666 (Sept. 24) 1938.

On account of their experience in the treatment of more than 200 patients suffering from encephalitis and related neurotropic infections of the nervous system with intravenous injections of a 40 per cent solution of methenamine (10 cc. injected at a time; total dose, 100 or 200 cc.) the authors recommend this treatment emphatically. Also they suggest it for patients suffering presumably from a neurotropic infection.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF MENINGITIS BY MEANS OF SULFANILAMIDE. J. E. MINKENHOF, Nederl. tijdschr. v. geneesk. **82**:4986 (Oct. 8) 1938.

A warning is given against overestimating therapeutic measures for meningococcic meningitis. The additional factors that can influence the prognosis (perhaps even more than the treatment) are briefly mentioned. Up till now the results cited in the literature and the author's own experience with sulfanilamide treatment are so encouraging that in his opinion this drug should not be withheld from subjects suffering from meningococcosis. Provisionally the administration should be intrathecal and (additionally) subcutaneous, intramuscular or oral. In other types of purulent meningitis the remedy is probably useful only when the disease is of streptococcic origin.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF CHOREA MINOR. S. KROONENBERG, Nederl. tijdschr. v. geneesk. **82**:4996 (Oct. 8) 1938.

For the treatment of chorea minor Kroonenberg advises the use of some calming medicines, especially phenobarbital, besides general measures for assuring rest and simple physical means. The use of phenylethylhydantoin cannot be recommended, nor does it seem advisable to use very potent medicines or physical methods. A survey is given of the results of treatment in 73 cases of chorea, observed in 56 patients.

VAN CREVELD, Amsterdam, Netherlands.

Psychology and Psychiatry

TOWARD THE DEVELOPMENT OF EMOTIONAL STABILITY—A CASE STUDY. CHILD RESEARCH CLINIC OF THE WOODS SCHOOLS, Child Research Clinic Pamphlet 5, 1937.

A 7 year old boy was admitted to the Woods Schools with the complaints of tics, temper tantrums, fears and mental retardation. During the six years in the school his intelligence quotient increased several points, he became more stable emotionally, the tics and temper tantrums disappeared, and his school work was satisfactory. He developed an interest in reading and music.

BEVERLY, Chicago.

READING DISABILITY—A CASE STUDY. CHILD RESEARCH CLINIC OF THE WOODS SCHOOLS, Child Research Clinic Pamphlet 7, 1937.

A 13 year old boy was admitted to the Woods Schools with the complaint that he was unable to read and difficult to manage. He was an adopted boy who had been in many schools. On admission he was found to have an intelligence quotient of 71 and about second grade reading ability. The report describes the test scores at various periods during his six months in the school. Reading improved one year and six months in a six month period; arithmetic gained one year in six months, and with special help spelling improved one year and eight months in six months.

BEVERLY, Chicago.

AMAUROTIC FAMILY IDIOCY. H. B. FITZ JERRELL and B. B. NEUCHILLER, Illinois M. J. **74**:456 (Nov.) 1938.

This is a report of 2 cases of amaurotic family idiocy occurring in the same family.

BARBOUR, Peoria, Ill.

THE PSYCHOLOGIC HYGIENE OF INFANT FEEDING. A. GESELL, Ment. Hyg. **22**:216 (April) 1938.

Because the deepest and most vital cravings of the infant have to do with food and sleep, his daily schedules of feeding and sleeping assume great psychologic significance. Only by individualizing the schedules can one meet the infant's organic needs promptly and fully. By meeting them with certainty, one multiplies the experiences of satisfied expectation which create an increasing sense of security. This "sense" is a patterned product of mental growth. It is not a vague essence but a structured orientation of the infant's total action system. It doubtless has a neurochemical basis as real as the physical basis of more objective patterns of behavior. The individualization of schedules for feeding and sleep in infancy, therefore, is essential to mental health. These conclusions are the results of an elaborate and painstaking series of experiments. All normal infants in their behavioral development tend to follow an autogenic sequence which is characteristic of the species. Equally important is recognition of the individual differences to give the infant a lead in initiating variations from day to day as a means of testing

and achieving. An inflexible schedule may result in a conflict between infant and adult, with resulting anxiety and frustration. The hygiene of infant feeding cannot be advanced on a physical basis alone, but the ubiquitous psychologic factors must be recognized and dealt with.

CORSON, Stockbridge, Mass. [ARCH. NEUROL. & PSYCHIAT.]

TRAINING OF THE PRE-SCHOOL CHILD. C. HEINIG, M. J. Australia **2**:155 (July 30) 1938.

According to Heinig, the justification of child training as practiced by teachers in nursery schools is predicated on two principles: (1) that human beings carry a heavy preventable load of physical defects and behavior problems which decrease their chances of happiness and their maximum efficiency; (2) that since prevention is in every way more economical and desirable than correction, and since lasting habits are acquired during the first six years of life, training in right beginnings should be given in the nursery years.

In the child training program described an attempt is made to carry over the program of mental, social and emotional development as seen and supervised in the nursery school into the home by including a considerable element of parental education.

Various technics are practiced in the nursery school: First, the child is placed in a safe mental environment in which he can satisfy his drive for physical activity; second, he is allowed to "do for himself," free from the thoughtless "don'ts" which are so apt to hamper development; third, he is encouraged to develop responsibility; fourth, he utilizes the well established premise of learning through doing; fifth, an effort is made to keep the environment alive and interesting; sixth, an attempt is made to utilize the "natural rhythms," i.e., periods of activity and periods of rest; seventh, emphasis is placed on success rather than on failure by giving adequate praise; and further, it is kept in mind that learning from peers is more wholesomely digested than learning from adults, that social contacts are desirable, that frequently guidance can be given best by some one not related, that biologically perfect parenthood does not mean necessarily psychologically informed parenthood, that parents need help in acquiring technic and that twenty-four hour intelligent guidance is desirable.

The schedule of preschool activities is given in some detail.

TENNEY, Madison, Wis.

HOW A HUNGARIAN GIRL AGED 7 LEARNED FRENCH. A. KENYERES, Arch. de psychol. **26**:322, 1938.

Detailed study of the language of a Hungarian girl who had moved with her parents and for whom a journal was kept showed that the strongest motivation for learning French came from a desire to play with her fellows. After six months she was using French and Hungarian to supplement each other, and after ten months she spoke French like a Swiss girl of her age, except for a few difficult verb forms. The learning of French differed significantly not only from normal learning of the use of the mother tongue but also from adult learning of foreign languages. The addition of a second language did not noticeably retard intellectual development.

HERRICK, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

LATE FORMS OF AMAUROTIC IDIOCY SHOWING THE PICTURE OF PARALYSIS AGITANS. J. HALLERVORDEN, Monatschr. f. Psychiat. u. Neurol. **99**:74 (April) 1938.

Late forms of amaurotic idiocy with varying clinical pictures have been described by a number of authors. In some instances the illness was preceded by earlier disturbances, such as mental deficiency; these cases are probably to be regarded as instances of late infantile or juvenile amaurotic idiocy with a pro-

tracted course and not as genuine cases of the late form of the disorder. However, a sharp separation between the two groups cannot be made. Hallervorden reports the case of a patient who had always been mentally deficient. At the age of 39 he was admitted to a hospital for mental diseases because of increasing mental disturbance. He showed a spastic gait, ataxic phenomena and dysarthria. Finally, there developed the neurologic picture of paralysis agitans, and the patient died, at the age of 54. The brain displayed distinct atrophy. Microscopic examination disclosed an abundance of large, balloon-like nerve cells, which contained lipoid droplets and were typical of amaurotic idiocy. They were observed throughout the brain but were most numerous in the corpus striatum, hypothalamus, thalamus and substantia nigra. Most of the Purkinje cells of the cerebellum had disappeared. In addition to these characteristic alterations, nerve cells exhibiting neurofibrillar lesions of the Alzheimer type were seen in the cornu ammonis, hypothalamus, thalamus and corpus striatum. Changes of this type, hitherto undescribed in cases of amaurotic idiocy, are not considered specific for senility; they are probably expressions of a particular kind of colloidal alteration of the nerve tissue, but their significance in the present case is obscure.

ROTHSCHILD, Foxborough, Mass. [ARCH. NEUROL. & PSYCHIAT.]

Diseases of the Genitourinary Tract

EFFECT OF IRRADIATION ON THE FUNCTION OF THE OVARY IN YOUNG GIRLS. I. I. KAPLAN, Am. J. Obst. & Gynec. **37**:158 (Jan.) 1939.

Kaplan reports the case of a 14 year old girl who at the age of 4 years received intensive roentgen and radium therapy for a pelvic tumor. Menstruation began at the age of 12 years and has been normal since the onset. He concludes that roentgen therapy is not necessarily destructive of ovarian tissues. The younger the patient the less probable is it that sterilization by irradiation will be permanent.

ARENA, Durham, N. C.

RUPTURE OF CONGENITAL SOLITARY KIDNEY. L. G. ERICKSEN, Am. J. Roentgenol. **39**:731 (May) 1938.

Ericksen emphasized the importance of determining the presence or the absence of the other kidney in cases of rupture of a kidney, before the removal of such a kidney. Absence or hypoplasia of a kidney occurs in 0.25 per cent of cases. Excretory or intravenous urographic examination is indicated in all such cases. Sometimes a flat roentgenogram will suggest the absence of a kidney or the presence of a very small one. Renal anomaly is often suggested and is accompanied by such apparent malformations as: rudimetary epididymis, atrophy or absence of the testicle, hypospadias, pseudohermaphrodism, vaginal defects or defects of the external genitalia. If there is doubt after study of an intravenous pyelogram, an attempt should be made to obtain a retrograde pyelogram of the unaffected side.

SQUIRE, Chicago.

NEPHROSIS TREATED BY THE OSMAN METHOD. H. LOWENBERG SR. and M. J. FREEDMAN, Arch. Pediat. **55**:435 (July) 1938.

High alkali therapy was employed in the treatment of nephrosis in a 5 year old girl and was followed by a symptomatic cure.

ORR, Buffalo.

WILMS' EMBRYOMA. R. O. STERN and G. H. NEWNS, Arch. Dis. Childhood **13**:193 (Sept.) 1938.

A series of 26 cases of Wilms' embryoma of the kidney is described, covering a period of seventeen years. This tumor was one and a half times as common in females as in males. All but 3 of the patients were below the age of 5 years, and 15 were under 3 years. The growth was commoner on the left than on the right side. One case was noted in which it occupied a median position and had both kidneys stretched over it. The onset was in most cases insidious, the commonest presenting symptom being enlargement of the abdomen. In 7 cases the onset was acute or subacute. Visceral metastases were uncommon, occurring in only a third of the patients who came to autopsy, and in these metastasis was not extensive. The results of nephrectomy in this series are encouraging; of the 16 patients operated on, 4 are still alive. It is suggested that a more hopeful prognosis may be given if patients are subjected to nephrectomy preceded and followed by treatment with roentgen rays of high voltage. KELLY, Milwaukee.

NEPHROTIC NEPHRITIS. H. L. WALLACE, Tr. Med.-Chir. Soc. Edinburgh, 1938, p. 188; in Edinburgh M. J., October 1938.

A girl of 7 years had shown considerable edema two years previously as well as pallor and ill health. She was then passing large quantities of albumin but apparently no blood. There was no disturbance of the nitrogen in the blood, but the cholesterol was elevated and the proteins lowered. She had been observed frequently during the last two years, during which the edema had been intermittent but the albuminuria constant. An attack of measles was followed by disappearance of the albuminuria and edema—a dramatic occurrence following an acute febrile illness, unexplained, which has been reported in the experience of others.

NEFF, Kansas City, Mo.

HEMATOCOLPOS WITH CONGENITAL IMPERFORATE HYMEN. E. RASPALL HIDALGO and R. E. MENENDEZ MOREL, Bol. coll. med. Camaguey **1**:36 (Oct.-Dec.) 1938.

A girl aged 15 years complained of pain in the hypogastrium, radiating toward the lumbar region. The condition began four or five months before admission to the hospital. At the time of admission it had suddenly caused more severe pain and swelling of the abdomen but no fever. A tumor was palpated below the umbilicus, and vaginal examination revealed an imperforate hymen with a distention indicative of retained blood. A longitudinal incision in the hymen evacuated approximately 900 cc. of chocolate-colored blood.

DWYER, Kansas City, Mo.

ATRESIA OF THE URETER AND AGENESIS OF THE KIDNEY. H. HUMBURSKY, Bratisl. lekár. listy **16**:529 (Dec.) 1936.

A short review of the literature is followed by a report of a case. A 2 year old girl with miliary tuberculosis had aplasia of the left kidney and of the pelvis of this kidney, agenesis of the left renal artery and vein and hypertrophy of the right kidney. The left ureter was not shortened; it was stenosed in the midportion but opened into the bladder. Aplasia of the left kidney is more common in the male and rarer in the female, with no predilection for either side.

STULIK, Chicago.

A Statistical Study of Cystitis in Children. Y. Kimura, Orient. J. Dis. Infants **23**:277 (March) 1938.

A statistical analysis was made of 243 cases of cystitis. The following observations were made:

1. Females are more susceptible to the disease than males (1:1.4).

2. Of the patients, 48.1 per cent were infants, and 84.7 per cent were children under 4 years of age.

3. The occurrence was seasonal (May-September), with a peak in July.

4. The colon bacillus was the predominating causative agent.

5. The disease was primary in only 24.4 per cent of the cases; in the remainder it was secondary to infections of the upper respiratory tract and nutritional disturbances.

6. The chief symptoms were remittent fever, vomiting, chill, malaise and convulsions.

7. Severe generalized symptoms were found mostly in young infants. Nervous manifestations were common in sucklings.

8. Localized symptoms were seen in older children, frequency in urination being the most important.

9. The urine was turbid and acid in reaction; it contained albumin, leukocytes and epithelial cells.

10. The blood picture was characterized by anemia, low hemoglobin, and leukocytosis due to relative neutrophilia and concomitant lymphocytopenia.

11. The duration of fever was usually two weeks, lysis characterizing its termination.

12. The mortality rate was 2.9 per cent.

13. Five patients showed a relapse.

14. In 9 patients the condition was chronic.

Kato, Chicago.

Duplication of the Urethra and Paravaginal Cyst. J. J. Brugman and E. A. Imminк, Nederl. tijdschr. v. geneesk. **82**:5755 (Dec. 3) 1938.

This is a description of a maldevelopment of the kidneys; there was duplication of the ureter, and one of the ureters ended in a paravaginal cyst.

van Creveld, Amsterdam, Netherlands.

Diseases of the Ductless Glands; Endocrinology

Calorigenic Potency of Free Thyroxine by Mouth. W. O. Thompson, P. K. Thompson, S. G. Taylor III and L. F. N. Dickie, Endocrinology **24**: 87 (Jan.) 1939.

The authors have previously shown that synthetic thyroxin administered by mouth in single doses of from 10 to 100 mg. does not produce a definite increase in basal metabolism in patients with myxedema. When administered by way of the duodenum in single doses of from 10 to 50 mg., it is likewise without demonstrable effect. On the other hand, it does produce a clearcut calorigenic repsonse when administered as the monosodium salt and a still greater effect when given in an alkaline solution. The present paper reports the effect of administering thyroxin orally as the free amino acid in large daily doses for a comparatively long period.

To a patient with marked myxedema, whose basal metabolism was minus 36 per cent, it was necessary to administer at least 50 mg. of thyroxin daily by mouth, as the free amino acid, in order to maintain metabolism at a normal level. On the basis of these data the authors hold that thyroxine given orally in this form is about one thirty-third as effective as when given orally in the form of the monosodium salt, about one ninetieth as effective as when given orally in alkaline solution and about one one hundred and fiftieth as effective as when given intravenously in alkaline solution.

If thyroxine is administered orally in the treatment of myxedema, it should be given in an alkaline solution in order to produce maximum results.

JACOBSEN, Buffalo.

PSEUDO-SEXUAL PRECOCITY: THE ADRENAL CORTICAL SYNDROME IN PREADOLESCENT GIRLS. W. A. REILLY, H. LISSER and F. HINMAN, Endocrinology **24**:91 (Jan.) 1939.

A case of pseudosexual precocity is reported in which a tumor of the adrenal gland was successfully removed. The child is apparently normal two years after operation.

A painstaking review of the literature on this syndrome in girls is given. Of the 20 patients with this syndrome in whom adrenalectomy was attempted, 10 died, a mortality of 50 per cent. Ten such operations were successful. All ten were done after 1924.

JACOBSEN, Buffalo.

LACTOGENIC HORMONE. A. A. WERNER, Endocrinology **24**:119 (Jan.) 1939.

Five castrate girls were treated with theelin (estrone) and with theelin and progesterone, to bring about development of the breasts, and with a lactogenic substance (Evans) to stimulate lactation.

The effect of theelin on the breasts was characterized by development of the glandular trees, enlargement of the breasts and sensations of fulness, with tingling and erection of the nipples. Progesterone exaggerated the effect of theelin. In 2 patients who received 6 and 4 injections of a lactogenic factor, respectively, the breasts were fuller and there was a sensation of trickling in the ducts and tingling in the nipples. None of the women lactated, as a sufficient amount of the lactogenic factor could not be given, owing to severe reactions.

The local reactions, accompanied by temperatures of 101 and 102 F., plus the severe anaphylactic reactions, indicate that the present preparations of lactogenic "hormone" are impure and unsafe for human use.

Further research to find the cause of these reactions and to purify the preparations of lactogenic substance is necessary.

JACOBSEN, Buffalo.

EFFECT OF PROLONGED TESTOSTERONE PROPIONATE ADMINISTRATION ON THE IMMATURE AND ADULT FEMALE RAT. M. MAZER and C. MAZER, Endocrinology **24**:175 (Feb.) 1939.

In the immature rat prolonged administration of testosterone propionate causes a decrease in the weight of the pituitary, adrenals, ovaries and uterine horns and inhibition of estrus with mucification of the vaginal epithelium. The deleterious effect of prolonged testosterone treatment on the ovaries is temporary. Restitution of structure and function occurs within twenty-nine days.

Evidence is drawn from the literature and the experiments described that the duration of treatment is the determining factor in the effect of testosterone on the ovaries; short treatment produces stimulation and prolonged treatment depression. It is considered that the ovarian atrophy described herein is secondary to pituitary inhibition.

JACOBSEN, Buffalo.

HUMAN SERUM RESPONSE TO GONADOTROPIC HORMONE (PREGNANCY URINE EXTRACT). W. SAPHIR, K. M. HOWELL and R. H. KUNSTADTER, Endocrinology **24**:182 (Feb.) 1939.

Serum from human beings receiving large doses of the gonadotropic factor from the urine of pregnant women (antuitrin S) was examined for the presence of "antihormone" and for complement fixation antibody.

It is concluded that human beings do not respond with either true antibody or "antihormone" formation following the injection of this gonadotropic substance.

JACOBSEN, Buffalo.

EXPERIMENTAL PHASES OF THE PINEAL PROBLEM. N. H. EINHORN and L. G. ROWNTREE, Endocrinology **24**:221 (Feb.) 1939.

Pinealectomy in successive generations of parent rats exercised no noteworthy effect on the growth or development of the offspring.

However, daily intraperitoneal administration of 1 cc. of pineal extract to successive generations of rats resulted in an increase in the frequency of breeding, an acceleration in the rate of somatic differentiation and a retardation in the rate of growth in the offspring of treated rats. These biologic effects are progressive, becoming more marked in successive generations under treatment.

JACOBSEN, Buffalo.

DAILY EXCRETION OF URINARY ANDROGENS IN NORMAL CHILDREN. I. T. NATHANSON, L. E. TOWNE and J. C. AUB, Endocrinology **24**:335 (March) 1939.

A study of the daily urinary excretion of androgens in girls and boys of varying age groups with a colorimetric method revealed that there is definite variation in androgen excretion from day to day but that it is not of an adequate magnitude to be considered physiologically significant. Young children show less variation than the preadolescent or adolescent group.

There is no evidence of cyclic excretion of the androgens. The excretion of androgens varies directly with increasing chronologic age and also with the physical maturity of the subject.

JACOBSEN, Buffalo.

PROGESTERONE IS ANDROGENIC. R. R. GREENE, M. W. BURRIL and A. C. IVY, Endocrinology **24**:351 (March) 1939.

Experiments with rats indicated that progesterone is androgenic.

JACOBSEN, Buffalo.

RENAL LESION IN HYPERPARATHYROIDISM. W. A. D. ANDERSON, Endocrinology **24**:372 (March) 1939.

Chronic hyperparathyroidism is associated with distinctive microscopic changes in the kidney: interstitial fibrosis, calcification and infiltration by lymphocytes and plasma cells, cystic tubular dilation thickening and sometimes calcification of tubular basement membranes, and relative absence of active glomerulitis or involvement of tubular epithelial cells. In individual cases this picture may be varied by calculus formation and superimposed ascending infection.

JACOBSEN, Buffalo.

VITAMIN A DEFICIENCY IN DISEASE OF THE THYROID GLAND: ITS DETECTION BY DARK ADAPTATION. M. G. WOHL and J. B. FELDMAN, Endocrinology **24**: 389 (March) 1939.

The dark adaptation method was used in an investigation of 59 patients with various endocrinopathies and 30 controls who did not have endocrine disorder for

deficiency of vitamin A. Of 20 patients with hyperthyroidism, 18, and of 7 with hypothyroidism, all evidenced pathologic dark adaptation. It is concluded that the thyroid hormone is essential for conversion of carotene and storage of vitamin A.

JACOBSEN, Buffalo.

THYROTOXICOSIS IN A CHILD AGED 6 YEARS; THYROIDECTOMY. F. D. HART, Proc. Roy. Soc. Med. **31**:1155 (Aug.) 1938.

The patient was healthy until July 1937, when the bowels became loose, and two months later the neck was noticed to be full and the eyes protuberant. She was put to rest at home, but the signs became more definite, and she began to lose weight. She was then admitted to the hospital. After three weeks' rest in the ward and treatment with bromides she failed to gain weight. In the fourth week she was given compound solution of iodine, 4 minims (0.25 cc.) three times daily, which was continued for nineteen days before operation. The child stood the operation well. Gas and oxygen were used as an anesthetic. The surgeon removed five eighths of the thyroid gland. The family history, the physical examination and the progress after operation are given in detail in the report.

WILLIAMSON, New Orleans.

THYMIC ASTHMA. F. LOMBARDI, J. de pediat. **5**:111 (April-May) 1938.

A general review of the subject is undertaken from the clinical and therapeutic point of view. The author believes that Paltauf's theory of "status lymphaticus" should be considered at present. A clinical case of thymic asthma in a Brazilian girl 1½ years of age is presented as typical. The child was successfully treated by means of radium.

SOTO, Habana, Cuba.

Diseases of the Muscles, Bones, Joints and Lymph Glands

BENIGN BONE LESIONS SHOWING SPINDLE CELL INVASION OF BONE. J. T. MURPHY, Am. J. Roentgenol. **39**:568 (April) 1938.

Four cases of low grade infection of bone are reported. The patients were aged 7, 14, 18 and 32 years. The lesions bore a striking resemblance clinically, microscopically and roentgenologically to giant cell tumor, osteitis fibrosa and even osteogenic sarcoma.

This chronic fibrous osteomyelitis is characterized by a rapidly growing, expansile, rarefying, often trabeculated bone tumor. Histologically, there is a mixture of round, spindle and giant cells with fibrous tissue. They often respond to roentgen therapy. The cases described involved the clavicle, femur, radius and femur.

SQUIRE, Chicago.

ROENTGENOLOGIC ASPECTS OF SPINA BIFIDA OCCULTA. R. J. DITTRICK, Am. J. Roentgenol. **39**:937 (June) 1938.

Dittrick strives to show that spina bifida occulta is not an uncommon disease and that it produces a variety of clinical pictures. Thirty-three cases comprise the series on which his observations were made.

Roentgenographic findings are recognized best when the patient is 6 years of age. The most common location of the malformation is in the upper sacral segments, first and second, and not in the fifth lumbar as commonly taught. The malformation may be an incomplete fusion of the postneural arch, but more common are defects varying in size from 2 to 12 mm., round, oval or irregular, situated usually on either side of the midline and frequently multiple.

In combination with the bony malformation there are within the spinal canal either masses of fat in contact with nerve roots of the cauda equina or bands of fibrous tissue extending between the ventral surface of the laminas and either the dura or the nerve roots.

Whenever the bony defects are demonstrable in the roentgenograms, it is practically certain that the intraspinal changes are also present.

The spinal fluid shows no change except for some increase in the number of lymphocytes.

The clinical findings in spina bifida occulta are as follows:

1. Muscular rheumatism consisting of pain and tenderness of the voluntary muscles of the hips and legs. In the majority of patients in the series mentioned, complete relief was obtained by operation.

2. Pain low in the back. It may radiate to the thighs, legs or feet or be confined to the lower part of the spine. All but 1 of 7 patients were relieved by operations.

3. Spastic paralysis. This is a rare clinical finding. Operation gave some improvement but not a complete cure.

4. Infantile paralysis. Spina bifida occulta probably plays only a part in this pathologic picture.

5. Osteomyelitis. In the patients in which this was observed the infection involved bones innervated by the lumbosacral plexus. The infection was thought due to a neurotrophic dysfunction. Three patients showed improvement, with healing of bones and closing of sinuses, following operation.

6. Visceral dysfunction:

   (*a*) Enuresis. Operation for this symptom gave uncertain results.

   (*b*) Menstrual dysfunction. Dysmenorrhea was the most frequent complaint. Operation helped 2 of 4 patients.

   (*c*) Constipation. A barium sulfate enema showed a colospasm involving the descending and the sigmoid colon. Following operation, in practically all cases there was a prompt return to normal bowel habits.

The author concludes that there is a definite clinical syndrome associated with spina bifida occulta, caused by the intraspinal pathologic condition.

SQUIRE, Chicago.

JUVENILE FEMORAL OSTEOCHONDRITIS WITH ENDOCRINE DIFFICULTIES. C. E. GRIGNON, Union méd. du Canada **67**:144 (Feb.) 1938.

A 9 year old boy was examined because of obesity, inability to walk and mental retardation. At the age of 7, when he complained of pain on walking, osteochondritis was diagnosed. Rest in bed and a diet high in vitamins and minerals were tried, without success. At 9 years he weighed 190 pounds (86 kg.). Most of his fat was on the trunk and girdle; his hands and teeth were of the hypopituitary type; his hair and skin were dry and coarse; the testes were undescended.

Treatment was begun with thyroid and an extract from the anterior lobe of the pituitary gland (antuitrin). After nine months he showed a remarkable loss of weight; the testes descended, and the osteochondritis showed evidence of healing. Treatment is being continued.

DAFFINEE, Boston.

A NEW LINE OF TREATMENT IN A CERTAIN TYPE OF ARTHRITIS: A PRELIMINARY COMMUNICATION. E. A. SHIPTON and L. J. A. PARR, M. J. Australia **2**:500 (Sept. 24) 1938.

Shipton and Parr report prompt and remarkable improvement in 2 cases of severe rheumatoid arthritis following intramuscular injections of cysteine. In

explanation the authors theorize about imperfect digestion of protein and disturbed secretion of mucus as a result of the achlorhydria which accompanies severe arthritis.

GONCE, Madison, Wis.

PATHOGENESIS AND NATURE OF PERTHES' DISEASE. S. NAGURA and S. KOSUGE, Arch. f. klin. Chir. **191**:347 (March) 1938.

Nagura and Kosuge produced experimentally the pathologic and roentgenographic picture of Perthes' disease by traumatizing locally the head of the femur in month old puppies. The course of the disease was studied at one, two, three and four days and at one, three, six and eight weeks. They feel that in the clinical disease the primary trauma is overlooked, and that a secondary trauma. occurring when the process is already under way, is falsely blamed.

DAFFINEE, Boston.

FUNNEL CHEST. K. STOLTE, Monatschr. f. Kinderh. **75**:358 (Sept.) 1938.

This is a brief clinical report on a well child who suffered paralysis of the abdominal recti muscles. Following this a typical funnel-shaped chest developed. Stolte advances the hypothesis that the recti help maintain the normal contour of the chest by opposing the pull of the diaphragm.

GERSTLEY, Chicago.

Diseases of the Eye

CONGENITAL FAMILIAL CATARACT WITH CHOLESTERIN DEPOSITS. M. RIAD BEY, Brit. J. Ophth. **22**:745 (Dec.) 1938.

Bey presents an interesting pedigree of a family with familial congenital cataract associated with deposits of cholesterol crystals. The ages of the 13 members examined ranged between 6 and 85 years. Of this group, 7 females and 2 males were affected. There was no history of consanguinity in their parents or of mental disturbances or convulsions.

The pedigree shows that the hereditary influence was strongly marked in the females and that the cataract was derived from an affected female by continuous descent in three generations.

No constitutional disease was found. There was no clinical evidence of hypoparathyroidism, hypothyroidism or myotonia atrophica. The presence of cataract and crystal formations was bilateral except in a patient who lost her left eye early in childhood, probably as a result of purulent ophthalmia. Owing to the similar clinical appearance of the cataracts in all the persons examined, one description seems to be adequate. With focal examination the cataract appeared to be composed of discrete or confluent, nearly circular white or gray opacities grouped toward the axial part of the lens in the position occupied by the suture lines. In some cases these opacities extended backward deep into the substance of the lens; in others, the opacities radiated tubelike forward and outward from the center. They terminated just short of the capsule of the lens. Numerous fine shining crystals were scattered in the middle of these opacities. The peripheral part of the lens was clear.

The slit lamp microscope revealed that the space between the anterior capsule and the zone of disjunction was clear. In some cases the optical section of a narrow beam localized the opacities and crystals as extending from the anterior deeply toward the posterior cortical zone. In others, it fell short of the posterior zone of the fetal nucleus.

With the broad beam the opacities appeared either as flattened disks, more densely opaque at the periphery than at the center, or as a target of gray and white circles. A few others were mulberry-like and looked diaphanous when examined by transillumination.

The iridescent crystals were arranged at different angles and in different planes. A few appeared to be embedded in the masses of lenticular opacities. The crystals looked like tiny broken glass fragments; they were rectangular, with a notch at one corner, and were curiously transparent. They were optically indistinguishable from cholesterol crystals. Neither the opacities nor the crystals were to be seen in the periphery of the lens but only in the axial portion.

One illustration accompanies the article.

The cataracts described and the one shown in the illustration resemble coralliform cataract. Verhoeff found in his own case and in that of Zentmayer that the deposits were crystallized lens protein.

ZENTMAYER, Philadelphia. [ARCH. OPHTH.].

ORTHOPTIC TREATMENT OF CONCOMITANT CONVERGENT STRABISMUS. J. R. ANDERSON and D. S. MANN, M. J. Australia **1**:59 (Jan. 14) 1939.

In a study of 81 patients with concomitant strabismus who were treated in private practice a distinction is made between those having normal retinal association and those not having it. Of 38 patients with convergent squint and normal retinal association treated orthoptically, 17 of 24 who were not operated on in addition to training were cured. Operation is used for cosmetic cure when training is impossible and is believed to hasten recovery when a large angle of squint exists with glasses. In this type of case early operation followed by training is recommended. Failures with training alone are attributed to insufficiency of regular training, to the age of the patient, to amblyopia and to ill health in patients with normal association.

Of 43 patients with dissociation, 33 were treated by training and operation, and 11 were cured. Ten patients operated on but not trained failed to acquire full binocular vision. Failures in these patients are attributed to the same causes noted for those with normal association, but the early onset of squint with late initiation of treatment is regarded as a large factor in these failures.

The authors define cure as (*a*) the attainment of orthophoria or (*b*) a heterophoria of 50 or less, with a good range of fusion and stereoscopic vision. They recommend that orthoptics be used for the accurate measurement of the angle of squint and as a highly satisfactory treatment of heterophoria.

GONCE, Madison, Wis.

A HITHERTO UNKNOWN HEREDITARY OCULAR DISEASE (DEGENERATIO HYALOIDEA-RETINALIS HEREDITARIA) OBSERVED IN THE CANTON OF ZURICH: REPORT OF CASES. H. WAGNER, Klin. Monatsbl. f. Augenh. **100**:840 (June) 1938.

Wagner reports the observation of a new ocular disease in 13 of 26 members of one family from 1934 on. A genealogy comprising three generations is appended. The disease originates in the retina and vitreous, appears to be congenital and offers no ophthalmoscopic evidence of inflammation. The following characteristic symptoms were found: The vitreous was optically clear, showing only a few isolated floating cords; a peculiar preretinal circular membrane in the equatorial section of the vitreous was noted in every patient. At the first glance it resembled a detached retina. Holes were observed in the membrane, which was well defined toward the periphery in some cases and in others extended into the ora serrata, without demarcation. In some instances the membrane, presenting a circular arrangement, was connected with the internal limiting membrane of the retina; it varied in size and protruded into the vitreous. The retinal vessels, especially the veins, were thin, and some were surrounded by white sheaths. Isolated pigment dots were observed in the periphery of the retina. Atrophy and sclerosis of the vessels occurred. Some of the patients presented pale, yellowish disks, and one of them presented complete white atrophy of the optic nerves. All of the patients were myopic, with myopic astigmatism of the cornea. Concentric contraction of the field of vision and reduced visual acuity were common to all; these

changes increased later, owing to lenticular opacities. Various degrees of reduced adaptation to dark were noted. All the patients except the youngest had peculiar opacities of the posterior cortex of the lens, later accompanied by nuclear cataract. Because of synchysis of the vitreous, extraction of the cataract was not advisable. Blindness may follow atrophy of the optic nerve in middle age. There were no cerebral disturbances. The youngest generation presented the largest number of sufferers from this disease; equal portions of the other two generations were afflicted and healthy, respectively. The disease is dominantly hereditary in the mendelian sense. Wagner is of the opinion that the spread of this disease can be and should be prevented.

STOLL, Cincinnati. [ARCH. OPHTH.]

OCULAR COMPLICATIONS IN RHEUMATISM. E. HASSLER, Monatschr. f. Kinderh. **77**:23 (Jan.) 1939.

Hassler reports 2 cases of Still's disease and 2 cases of acute polyarthritis. In all these cases iritis occurred as a complication. His observation of such a complication in both diseases leads him to suggest that these diseases have similar etiologic factors.

GERSTLEY, Chicago.

Skin Diseases; Allergy

HYDROA ESTIVALE IN CONGENITAL PORPHYRIA. C. H. PEACHEY, K. DOBRINER and W. H. STRAIN, New York State J. Med. **38**:848 (June 1) 1938.

Hydroa aestivale due to congenital porphyria occurred in a 3 year old girl. Her face and the backs of her hands presented pink and red lesions. There were a few thick-walled vesicles. Both index fingers had lost the nails. The arms and legs showed excessive growth of hair. The cutaneous lesions appeared in the spring and summer and were due to photosensitivity. The urine was found to have a Burgundy wine color, due to the presence of large amounts of free porphyrin in it. The teeth were stained purplish or reddish brown. Roentgenographic examinations showed cystic changes in the ends of the long bones.

Liver therapy was given a thorough trial, and there was some temporary improvement. After cessation of this treatment the excretion of porphyrin returned to the original levels. It was not possible to study the child adequately for photosensitivity.

AIKMAN, Rochester, N. Y.

SOME EXPERIENCES WITH THE MERCURY VAPOUR LAMP. T. M. DOLAN, Brit. J. Phys. Med. **1**:282 (Aug.) 1938.

Dolan described the case of a boy who was completely cured of alopecia areata in eight weeks with weekly ultraviolet ray treatments. Sufficient amounts were given to keep the scalp red. He claims that one application of a sufficient amount of ultraviolet rays to cause third degree blistering will cure tinea corporis.

HARTMAN, Cleveland.

WHITE FORELOCK: A NEW MUTATION. A. M. NUSSEY, Lancet **2**:947 (Oct. 22) 1938.

Cockayne in 1933 divided persons with white forelocks into (1) piebald persons (having unpigmented patches of skin in addition to the white forelock) and (2) persons with white forelock only. In both these groups the abnormality is present at birth and as a dominant character is handed down direct from generation to generation. Occasionally the white forelock appears as a mutation in a family in which no such abnormality was known before, but, once established, its transmission occurs in the usual dominant fashion. Pearson recorded such an instance, and now Nussey records such a case of white forelock in a 10 year old boy.

LANGMANN, New York.

MULTIPLE CUTANEOUS ABSCESS WITH RECURRENCE IN A NURSLING. A. BERAUD, Arch. de méd. d. enf. **41**:736 (Nov.) 1938.

A girl 1 year of age suffered from multiple abscess of the scalp. The parents had both sustained attacks of furunculosis, and the mother's blood, fortified by specific and polyvalent vaccines, was used for immunotransfusion. This method of treatment had been successfully used by the author in many previous cases, including that of a sister of the patient, but in the present instance it resulted in complete failure. After a short period of relief, a succession of abscesses appeared over the neck and body. At this point the management was changed and antistaphylococcic anatoxin substituted for the hemotherapy. The amount injected was gradually increased from 0.2 to 0.7 cc. Recovery was rapid and permanent.

AMESSE, Denver.

ECTHYMA IN A YEAR OLD CHILD. G. CARDELLE, B. SANCHEZ SANTIAGO and A. GARCIA LOPEZ, Arch. de med. inf. **8**:380 (Sept.) 1938.

A year old child, breast fed, presented on the posterior part of the body, a series of ulcerous sores, each the size of the palm of the hand. They had a raised red border and exuded a purulent discharge. Cultures showed a gram-positive diplococcus, and Streptococcus haemolyticus. Cure was effected with methyl rosaniline and transfusions. The authors consider this to be an ecthyma, and not cutaneous gangrene.

SANFORD, Chicago.

PEMPHIGUS VULGARIS IN CHILDREN. J. MAY and others, Arch. de pediat. d. Uruguay **9**:500 (Aug.) 1938.

A case of pemphigus vulgaris is described. The main lesions were vesicles and blebs of various sizes, containing a clear fluid and later purulent. Medication did not improve the condition. The prognosis was favorable.

SCHLUTZ, Chicago.

INCOMPATIBILITY OF MOTHER'S MILK OBTAINED DURING MENSTRUATION, IN AN INFANT WITH EXUDATIVE DIATHESIS. J. W. CAMERER, Kinderärztl. Praxis **9**:372 (Sept.) 1938.

In a breast-fed infant 3 months of age "cradle cap" developed whenever the mother menstruated. Edema of the upper lip and of the eyelids, as well as diarrhea, accompanied the aggravation of cutaneous symptoms (eczema on the cheeks). After menstruation ceased, the edema and eczema in the infant disappeared to reappear as soon as the mother started to menstruate again. At the time of the mother's menstruation the infant showed eosinophilia, 26 per cent of the white blood cells being eosinophils. The author refers to Epstein's observation of urticaria in one of his patients under the same conditions.

HEYMANN, Cleveland.

A FLAVINE DYE IN THE NONINFECTIOUS ECZEMA OF CHILDHOOD. K. OXENIUS, München. med. Wchnschr. **84**:2062 (Dec. 24) 1937.

Oxenius has found that the application of a zinc paste containing 1 per cent rivanol (a flavine dyè) gives good results in moist as well as in dry eczema. The paste is spread on lint and kept in close contact with the skin. In the occasional case in which the secretion is excessive it may be desirable to apply wet dressings first.

BRAHDY, Mount Vernon, N. Y.

Surgery and Orthopedics

LOCAL ANESTHESIA IN CHILDREN. M. MOLITCH, Arch. Pediat. **55**:506 (Aug.) 1938.

Altogether, 847 tonsillectomies, 845 adenoidectomies and 322 circumcisions were done under local anesthesia on boys between the ages of 8 and 17.

There were no complications and no fatalities, and the children tolerated local anesthesia better than did adults.

ORR, Buffalo.

SOME COMMON POSTURAL DEFORMITIES AND THEIR TREATMENT BY EXERCISES AND MANIPULATION. E. CYRIAX, Brit. J. Phys. Med. **1**:202 (June) 1938.

Cyriax believes that in good posture a perpendicular line dropped from the ear or just behind it passes consecutively through the center of the shoulder joint, the center of the hip joint and the center of the ankle joint. He classifies postural deformities as voluntary, semivoluntary and involuntary, the last group being by far the largest.

He discusses the causes of the various deformities of the vertebral column, of the pelvis and of the lower extremities. With exception of those caused by disease, most deformities are caused by weakness of muscles or of muscle groups. The therapy depends on determining the muscles involved and the development of these muscles. A few methods are suggested.

He also discusses malrotation of vertebrae as a cause of some deformities and claims that reposition can be obtained in most cases "quite painlessly by manipulation without the use of any anesthetic."

HARTMAN, Cleveland.

TRANSFUSIONS IN PEDIATRIC ORTHOPEDICS. P. SANCHEZ TOLEDO, Arch. de med. inf. **8**:149 (April-June) 1939.

Transfusion is used as a preliminary to almost every form of orthopedic operation that requires any considerable traumatism of the tissues. The author believes that the transfused blood prevents shock. In acute osteomyelitis and in staphylococcic infections repeated small transfusion are of the utmost value.

SANFORD, Chicago.

SURGICAL TREATMENT OF MALFORMATIONS AND ITS RELATION TO THE LAW REGARDING PREVENTION OF HEREDITARY DISEASES. G. MARX, Arch. f. klin. Chir. **192**:645 (Sept.) 1938.

With a short discussion as to which malformations fall under the provisions of the law, Marx discusses and describes the surgical treatment of atresias of the anus and rectum, hypospadias, ectopia of the bladder, umbilical hernia, hemangioma, polydactylism, syndactylism and ectrodactylism.

DAFFINEE, Boston.

CANCEROUS SCARS OF BURNS. H. V. HASSELBACH, Beitr. z. klin. Chir. **164**:264, 1936.

Hasselbach reports a case of carcinoma developing at the sites of scars resulting from third degree burns in a 16 year old girl. Other cases, involving older persons, are reported.

RUBIN, Boston.

Teeth and Dentistry

DIET AND ITS RELATION TO DENTAL DISEASE. P. R. SHEPHERD, Brit. J. Phys. Med. **1**:243 (July) 1938.

Shepherd discusses chiefly the local effect of food on the gums and teeth in the causation of dental caries and pyorrhea. No experimental work or new idea is presented.

HARTMAN, Cleveland.

PREVENTIVE DENTISTRY IN THE PRE-SCHOOL PERIOD AND DURING FOETAL LIFE. M. ALY OSMAN, J. Egyptian M. A. **21**:388 (June) 1938.

This paper is rather general. The writer mentions the necessity of proper diet and the proper vitamin intake for the pregnant woman and later for the baby, to insure good teeth. A plea is made for close cooperation between physicians and dentists.

MULHERIN, Augusta, Ga.

PREVENTION OF DENTAL CARIES. F. HAMBURGER and H. GOLL, Med. Klin. **34**: 1115 (Aug. 26) 1938.

Hamburger and Goll discuss various possible causes of dental caries and conclude that the etiologic agent is multiple. They regard vitamin B deficiency as of especial importance and advocate widespread use of grain germ and dry yeast in the diet. They urge that studies be made with particular reference to the teeth of children whose mothers received such a diet during pregnancy and lactation.

The toothbrush is regarded as useless in preventing caries.

SIEMSEN, Chicago.

METABOLISM IN DENTAL DECAY AND PROPHYLAXIS AGAINST CARIES. I. JUNDELL, R. HANSON and T. SANDBERG, Acta pædiat. **23**:141, 1938.

One hundred and seventy-two children in a modern sanatorium for the treatment of patients with tuberculosis of bone were divided impartially into two groups: The members of the first group, which numbered 118 children of an average age of 12.9 years, received large daily supplements of cod liver oil or ultraviolet radiation; the members of the second, or control, group, numbering 44, of an average age of 13 years, ate a well balanced diet but received no supplement. During an average period of observation of fifteen and one-tenth months dental caries developed in the members of the first, or treated, group at the mean rate of 0.27 carious surface per month; during an average period of observation of thirteen and two-tenths months new carious surfaces developed in the untreated control children at the mean rate of 0.30 per month. That the diet was adequate from the point of view of its calcium and phosphorus content was demonstrated by the recalcification of osteoporotic bone in several patients with orthopedic tuberculosis treated in the same institution during the same period. The conclusion is drawn that measures aimed at improving the retention of calcium and phosphorus do not reduce the incidence of dental caries in already calcified portions of the teeth.

MCCUNE, New York.

Miscellaneous

MODE OF ACTION, CLINICAL USE AND TOXIC MANIFESTATIONS OF SULFANILAMIDE. P. H. LONG, E. A. BLISS and W. H. FEINSTONE, J. A. M. A. **112**:115 (Jan. 14) 1939.

By administering sulfanilamide and sulfone compounds along with pneumococci intraperitoneally to mice, the authors demonstrated that their earlier observation of a bacteriostatic effect is correct. When type-specific serum was used in conjunction, phagocytosis was increased. Factors concerning the use of sulfanilamide were also determined experimentally. The larger doses delayed the time of death. The same daily dose given in divided amounts decreased the mortality. The dosages required for severe and moderate infections are estimated from the clinical studies and given in tables, also the urinary concentrations required for various organisms. Proportionately, children require higher doses than adults, the size of doses being largely determined by the fluid intake. Intraspinal administration does not seem necessary. Saline cathartics are contraindicated.

The toxic symptoms observed among 408 treated patients are enumerated and evaluated.

HEERSMA, Kalamazoo, Mich.

ACETARSONE (STOVARSOL) INTOXICATION. E. S. PRADERA, Bol. Soc. cubana de pediat. **10**:340 (June) 1938.

A review is made of acetarsone (stovarsol) poisoning, with emphasis on the nervous complications. The case of a 6 month old child is presented, who received a total of 6.3 Gm. of acetarsone by mouth. Toxic symptoms appeared in the sixth week of treatment in the form of peripheral neuritis. Recovery occurred in six months.

Two other cases are described in which diarrhea, fever and cutaneous rash developed.

SCHLUTZ, Chicago.

A FURTHER REPORT ON CORN RUST POISONING IN CHILDHOOD. E. MAYERHOFER and B. DRAGISIC, Ztschr. f. Kinderh. **59**:543 (April 2) 1938.

The disorder results from the consumption of cheap corn meal. It is seen chiefly in infants and children of poor families. The patients present a rather complex array of symptoms, varying with the stage of the disease. These may involve the gastrointestinal tract, skin, mucous membranes, cardiovascular system or the nervous system. Of especial importance are the circulatory disturbances in the hands and feet; burning and itching of the palms and soles, swelling, and redness alternating with pallor may be present. Desquamation or gangrene may supervene. The toxic effect is due to a substance similar to ergotamine. A similar picture can be produced in mice. If proper dietary management is instituted recovery usually follows in a few weeks.

SIEMSEN, Chicago.

EFFECT OF CLIMATE ON CONVALESCENT CHILDREN. G. KLIEBERT and L. ZSELYONKA, Orvosi hetil. **82**:36 (Jan. 8) 1938.

The authors investigated the changes in the vegetative nervous system of convalescent children by taking the pulse rate at the beginning and at the end of convalescence. They found three groups: (1) children whose pulse rate rose at the end of convalescence (vagotonic children, most of whom gained in weight); (2) children whose pulse rate was slightly lower, and (3) children (the smallest group) in whom no changes were found. The authors found that the climate has a regulative effect on the vegetative nervous system. This effect changes in every climatic resort and is due to microclimatic influences.

GÖTTCHE, Budapest, Hungary.

CASES OF POISONING IN CHILDHOOD. L. FODOR and G. HELLER, Orvosi hetil. **82**:557 (June 4) 1938.

In a children's hospital in Budapest 316 children suffering from poisoning have been observed in eight years. In the greatest number of these patients poisoning occurred through carelessness and lack of supervision. Furthermore, the poisoning was often due to drugs being exchanged by mistake. The mortality rate was 12.9 per cent. Most of these patients had esophagitis caused by caustic alkalis (196 patients, with a mortality rate of 14.3 per cent). There were strikingly many with mushroom poisoning (25, of whom 5 died). It is furthermore interesting that in 9 children alcohol was the cause of poisoning; 2 of these children died. (A 2 year old boy drank 200 Gm. of rum and died two hours later.)

GÖTTCHE, Budapest, Hungary.

Society Transactions

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

R. R. MacGregor, M.D., *President*

Seventeenth Annual Meeting, Thousand Islands Club, Alexandria Bay, New York, June 16 and 17, 1939

Elizabeth Chant Robertson, M.D., *Secretary-Treasurer*

First Session

Friday Morning, June 16

Presidential Address. Dr. R. R. MacGregor, Kingston, Ontario.

In Vitro Experiments on the Effect of Added Blood Serum and Blood Plasma on the Sedimentation Rate. Dr. R. R. Struthers and Dr. H. L. Bacal, Montreal.

The sedimentation rate is probably the most delicate indicator of the activity of rheumatic fever and its various manifestations, in that it is the last value to return to a normal level after activity. We have formed the opinion that rheumatic infection should be divided into three types, according to the behavior of the sedimentation rate: 1. Acute rheumatic fever is a manifestion in which the sedimentation rate falls rapidly from a high to a normal level after the subsidence of symptoms. 2. Chorea is a manifestation in which the sedimentation rate is constantly normal in the absence of complications. 3. Carditis is a manifestation in which with recovery the sedimentation rate falls slowly, during a period of months, to a normal level. Because of the last-mentioned phenomenon these studies were undertaken, in the hope that the addition of either blood serum or blood plasma to the samples used in determining the sedimentation rate would influence the rate to approximate normal levels in a shorter time. Should such be the case, the giving of either blood serum or blood plasma to a patient with active rheumatic infection would cause the sedimentation rate to be less rapid and perhaps through some process would lessen the activity of the infection.

In all these in vitro experiments the patients used had active rheumatic involvement with high sedimentation rates. The controls had no history of rheumatism, had normal sedimentation rates and were of blood groups compatible with those of the patients.

Effect of Blood Serum on the Sedimentation Rate.—Four patients and 4 controls were used. Since the addition of serum to the samples set up for testing the sedimentation rate caused them to clot, this method of experimentation had to be stopped.

Effect of Blood Plasma on the Sedimentation Rate.—Twenty-seven patients and 27 controls were used. In 17 of the 27 experiments the addition of normal plasma to the samples obtained from the rheumatic patients resulted in a decreased or lowered sedimentation rate. In 4 cases the value was below the original level.

Clinical Application.—Three patients with rheumatic fever complicated by carditis and other rheumatic manifestations were given blood plasma intravenously. These particular subjects were selected because of the severity and frequent complications of the disease and because of failure of the sedimentation rate to return

to normal within a reasonable and average time. Although we cannot draw any definite conclusions as to the value of blood plasma transfusions in cases of active rheumatic carditis, it is felt that in certain selected cases the clinical course and the activity of the infection might be shortened.

DISCUSSION

DR. ALTON GOLDBLOOM, Montreal: In spite of Dr. Bacal's experiment with serum in vitro, I think it would be interesting to know, if he has tested it, the effect of administration of serum on these patients and the effect of simple blood transfusion on the sedimentation rates of patients with rheumatic fever.

DR. J. D. KEITH, Toronto: The idea of transfusion has been suggested before. Dr. Bacal's idea of establishing a definite scientific basis for the use of transfusions is good. I am not sure that one should use the sedimentation rate as the criterion of improvement; that is, if it falls this is not necessarily a sign that the patient is improving. Jones, of Boston, has shown that the white blood count is often elevated when the sedimentation rate is down. A low rate does not always mean that the patient has recovered. Similarly, a sedimentation rate may become normal when heart failure supervenes in rheumatic fever. The factors associated with the change in sedimentation rate are numerous. I have given sodium nitrite to patients with high sedimentation rates; this lowered the values, but it did not produce any improvement. Transfusion has been used in Philadelphia for a large number of rheumatic patients. I have not seen a report of the work, but it was stated that no remarkable improvement was noticed.

DR. H. L. BACAL, Montreal: As regards Dr. Goldbloom's question on the effect of simple transfusions on the course of rheumatic fever, Dr. Weiss of New York reported 2 cases in which he obtained marvelous results. He reported only the 2 cases, and he had no controls. The patients might have recovered without therapy. As regards blood serum, we have not tried it for patients, but of course it would not have any untoward effect on them. The experiments in vitro were ruined by the clotting. Regarding the question of Dr. Keith, we agree with him heartily. We know that a fall in the sedimentation rate will indicate cardiac decompensation before it can be diagnosed clinically. The sedimentation rate falls by crises. Under these circumstances this generally indicates a poor prognosis. We agree with what Dr. Keith said in regard to the other cases. We should like, however, to see the blood plasma given intravenously in cases of severe, long-protracted rheumatic carditis to see what happens. We do not feel that just because we lower the sedimentation rate the patient's condition is actually improving. All the criteria in these cases should be considered.

METABOLISM OF LACTIC ACID IN ACUTE RHEUMATIC FEVER. DR. J. D. KEITH, Toronto.

(The historical association between lactic acid metabolism and rheumatic fever was briefly reviewed.) The recent investigations of Lovatt Evans and others have emphasized the importance of lactic acid in normal cardiac nutrition. A group of 17 control patients who were suffering from a variety of acute and chronic diseases were studied by determinations of the lactic acid content of the blood and urine. The values were compared with similar determinations for a group of 17 children suffering from rheumatic carditis, which were made on admission and repeatedly during their stay in the hospital. The average on admission was noticeably higher than the average for the controls. In consideration of the known physiology of lactic acid metabolism and the pathologic features of rheumatic carditis, it is suggested that this was due to the myocardial damage and the vascular change, to involvement of the liver or to both. A vasodilator was used in an attempt to elucidate this point, but no difference was found between the rheumatic group and the controls.

DISCUSSION

DR. F. F. TISDALL, Toronto: This paper is of considerable interest in indicating another possible approach to the study of this complicated subject, and any new approach is certainly welcome.

DR. S. GRAHAM ROSS, Montreal: Did the control patients have infections?

DR. J. D. KEITH, Toronto: The 17 control patients represented the average variety of diseases, other than rheumatism, to be found in a hospital. Most of them did have infection. Some had cervical adenitis, some had empyema and 1 or 2 had tuberculous lesions. All these conditions will, I believe, tend to elevate the lactic acid value slightly. I have no group of strictly normal children to compare with these controls, and the figures for lactic acid in the blood of my control group were a little higher than those usually stated to be normal in the literature. In several respects the controls I used were preferable to normal children.

NEW METHOD OF OBTAINING SPUTUM FROM INFANTS AND CHILDREN THOUGHT TO HAVE PNEUMOCOCCI IN THE NASOPHARYNX. DR. W. J. AUGER, Toronto.

A suction method of obtaining sputum from infants and children has been devised to replace the laryngeal swab technic. With one attempt it is usually possible to obtain sufficient sputum from the larynx or nasopharynx for direct examination and cultural purposes. Preliminary broth culturing is not necessary. The apparatus consists of a glass syringe, a catheter and a simple valve arrangement which permits powerful intermittent suction.

Sputum from the nasopharynx of an infant or child has been found ideal for typing pneumococci in a case of early severe pneumococcic pneumonia, while sputum from the larynx is more suitable for diagnosis in a case of tuberculosis, whooping cough or pneumonia due to a mixed infection.

DISCUSSION

DR. R. R. MACGREGOR, Kingston, Ontario: A research fellow in Queen's University Faculty of Medicine has been using an apparatus somewhat simpler than this and has found it effective. It is a simple syringe with a catheter attached. The catheter is pushed into the back of the throat until the child coughs, and there is no difficulty in getting sufficient sputum. The 25 per cent incidence of empyema that Dr. Auger cited seems high, even in hospital practice.

DR. W. J. AUGER, Toronto: I should have said that 25 per cent refers to type I pneumonia only.

LOCALIZED BULLOUS EMPHYSEMA ASSOCIATED WITH PNEUMONIA IN CHILDREN. DR. B. BENJAMIN and DR. A. E. CHILDE, Montreal.

The condition of localized bullous emphysema associated with pneumonia has been practically overlooked, even in the more recently published pediatric textbooks. It is certainly common enough to warrant a complete description in all volumes dealing with the diagnosis of diseases of the lung in infants and children. The terms "cyst" and "cystic" should not be applied to this condition. In contrast, true congenital pulmonary air cyst is encountered rarely. It should be emphasized that in all our cases emphysema has been associated with pneumonia and frequently with some degree of pleurisy, often localized in the affected region. There may be accompanying empyema or, if rupture of the pleura occurs, pneumothorax. We have not encountered emphysema in children with pulmonary tuberculosis without pneumonia; nor have we observed any instance of it in roentgenograms of normal children's chests. The characteristic roentgen appearance of localized bullous emphysema consists of one or more abnormal areas of diminished density, surrounded by thin dense smooth margins. These areas are spheroid or ovoid and are sometimes loculated. They are easily seen when the surrounding lung is comparatively clear; on the other hand, they may be merely suspected at first,

when infiltration is present in the contiguous lung, but they become more definite as this clears in subsequent examinations. Their location is usually subpleural or intrapleural. They may contain fluid, but as a rule only a small amount is present. The involvement varies in size from small areas, which may be hardly distinguishable, to voluminous, balloon-like spaces, which may occupy a large portion of one lung. Variations in size occur from time to time until they eventually disappear. Usually this takes place in a few weeks, but occasionally some months may elapse before the chest returns to a normal status.

This condition is not accompanied by any abnormal signs or symptoms, unless enormous inflation results or the pleura ruptures, with the formation of pneumothorax, which gives evidence of increased intrathoracic pressure.

The differential diagnosis between bullous emphysema and pulmonary abscess, localized pneumothorax, congenital pulmonary air cyst and diaphragmatic hernia is not difficult, if the patient can be followed for a short time.

No treatment is necessary unless complicating conditions ensue.

DISCUSSION

Dr. N. Silverthorne, Toronto: I have observed similar annular shadows in the chests of children recovering from pneumonia not associated with any specific disease. I was interested in Dr. Benjamin's theory as to how they disappeared. In the few cases I have observed their disappearance was slow.

Dr. J. B. Scriver, Montreal: In Montreal, in one of the wards for newborn infants, an infant went into sudden collapse, and roentgen examination showed massive atelectasis. A week later it showed one of these annular shadows. The baby was extremely ill for two weeks and then recovered, and during the course of the next five months this shadow slowly disappeared. The child is now 2 years old and is completely well.

Dr. S. Graham Ross, Montreal: One of the interesting things about these cases is the number in which fluid collects. Formerly this was thought to indicate necrosis with abscess formation, but apparently, according to Dr. Benjamin and Dr. Caffey, who recently reported some cases, although this collection of fluid is common the condition clears without abscess formation.

Dr. A. P. Hart, Toronto: I confirm from my own experience what Dr. Ross has said. I have had 1 or 2 of these cases. One patient had a quantity of fluid, which disappeared slowly. Sterile fluid was drawn off once or twice. The children are now apparently entirely well.

Dr. S. Graham Ross, Montreal: Dr. Benjamin, do such obstructive emphysematous lobular lesions appear in pertussis pneumonia?

Dr. B. Benjamin, Montreal: The outcome in the cases mentioned shows well that although some years ago the condition would have been labeled cysts, if nothing untoward is done the children gradually recover. With regard to Dr. Ross's question, I can say only that children with whooping cough are not admitted to the hospital if it can be prevented. In the literature, so far as I have been able to find, there is little mention of this condition as associated with pertussis pneumonia in children. I did not mention a number of reported series of adults and of some children with this condition. Adults show these annular shadows, which are usually wrongly diagnosed. Only 1 child, with the severest involvement, which in the first place I was inclined to call a cyst, contracted whooping cough and was studied roentgenographically. There was absolutely nothing abnormal in the chest, and the follow-up roentgenogram made some years later was practically clear.

Vitamin C Requirements of Infants. Dr. C. E. Snelling, Toronto.

A series of measurements of the plasma ascorbic acid in infants and children was made, and later ascorbic acid was administered by mouth to determine its effect on the plasma ascorbic acid.

Breast-fed infants have higher values for plasma ascorbic acid than artificially fed babies receiving 2 ounces (60 cc.) of orange juice regularly. The latter have higher levels than the patients not receiving orange juice or a similar vitamin C supplement. Many artificially fed infants have extremely low levels of plasma ascorbic acid with no clinical evidence of scurvy. Children 2 to 14 years old have values of the same magnitude as those of breast-fed infants.

Low values for plasma ascorbic acid by themselves do not give the picture of the general ascorbic acid nutrition of the subject and cannot be used as a standard for the diagnosis of scurvy.

DISCUSSION

DR. T. G. H. DRAKE, Toronto: Dr. Snelling is to be commended for making this huge number of measurements. In the past there has been a great difference between measurements of blood ascorbic acid reported for normal persons by various observers. This may be due to the methods of collection and analysis. I should like Dr. Snelling to point out the essential precautions one must take in the collection and preservation of the blood before analysis.

DR. F. F. TISDALL, Toronto: Dr. Snelling's work has a definite clinical application. He has shown that infants may have no measurable ascorbic acid in their blood when scurvy is developing, when it is healing and when it is not present at all. He has also shown that administration of 2 ounces of orange juice daily to artificially fed infants results in an average ascorbic acid level of 0.3 mg. per hundred cubic centimeters, whereas the breast-fed infant has a level more than twice as high, 0.75 mg. Two weeks ago in New York, at the American Academy of Pediatrics, Dr. Bakwin presented a most interesting paper along similar lines in which he reported exactly the same findings. On further investigation he found that when he gave ascorbic acid, either pure or as orange juice, in divided doses the ascorbic acid levels of the blood were higher. When given in one dose, it is probably partially excreted or not utilized by the body. One must first of all consider what level is safe. Is it 0.75 mg. per hundred cubic centimeters, or is one justified in giving 1 or 2 ounces of orange juice daily, which maintains a level of 0.3 mg.? One should aim to keep the level up to that of breast-fed infants. Some form of ascorbic acid medication should be started shortly after birth and not three or four months after, as has been the custom. It may be wise to give it in two or three doses daily rather than in a single dose.

DR. C. E. SNELLING, Toronto: I was pleased to hear that Dr. Bakwin's findings fitted in with our results. As for Dr. Drake's question regarding the method of collection and analysis, any one who is familiar with the literature on ascorbic acid measurements will immediately realize its importance. As Dr. Jackson pointed out at this meeting a year ago, one encounters many pitfalls when working with this determination. Until a year or two ago the majority of papers published were of little value because the necessary precautions were not taken. These we have particularly stressed. The blood was obtained by venipuncture and put into tubes with 2 drops of a 20 per cent solution of potassium oxalate and 1 drop of a 5 per cent solution of potassium cyanide to each 5 cc. of blood; the liquids were mixed and immediately chilled. It is most important to do this quickly to stop any action of the red blood cells in using up the ascorbic acid present. Certain objections have been raised to the use of cyanide. It has been found that cyanide has additional reducing factors, but if the cyanide is pure or old it does not have this effect. Dr. Jackson tested the cyanide we are using, and there was no change in the reading. One of the most important precautions is the avoidance of hemolysis. One reads that a wet syringe is one of the main causes, but we have found that the greatest cause of hemolysis in our work was too great suction in the withdrawal of the blood or too much pressure in transferring the blood from the syringe to the tube. In particular, one should remove the needle before transferring the blood. The measurements on the plasma were made with the Evelyn photoelectric colorimeter. The blood had been kept chilled, and the measurement was made as soon as possible. Dichlorophenolindophenol was used as an indicator.

VITAMIN D INTOXICATION IN INFANCY. DR. S. GRAHAM ROSS and DR. W. E. WILLIAMS, Montreal.

Four cases of hypervitaminosis D are reported in which there were two recoveries and two deaths. Permission for one autopsy was obtained. The ages ranged from 8 to 14 months. The vitamin had been administered over several months as irradiated ergosterol in doses of 20,000 to 40,000 international (U. S. P.) units daily. The symptoms in all cases were anorexia, loss of weight and vomiting.

The first patient was admitted for pyelonephritis. The findings were malnutrition, weakness, muscular hypotonia, peripheral facial palsy and anemia. The urine contained albumin, pus and casts. Chemical examination of the blood showed increased nonprotein nitrogen, hypercholesteremia and 18 mg. of serum calcium and 5.1 mg. of inorganic phosphorus per hundred cubic centimeters. Roentgenograms of the long bones showed increased density at the zone of provisional calcification; proximal to this was a zone of rarefaction and proximal to this a zone of increased density. The zone of rarefaction increased in width during the stay in the hospital. Generalized periosteal thickening was present in most of the bones of the body, with a dense outer layer and a rarefied area between this and the dense bone. Urinary excretion of calcium was increased, even with a low calcium diet. Administration of vitamin D was stopped, which was followed by a gradual improvement. The serum calcium gradually dropped to a normal level, the urine cleared, and a year later the roentgenograms showed normal bones.

The second case was similar to the first, but involvement was milder. Hypercalcemia was present. The kidneys were not affected, and the long bones showed merely increased density in the zone of provisional calcification. Recovery was rapid, and hypercalcemia had disappeared in several months.

The last 2 patients were premature twins. One was admitted to the hospital with bronchopneumonia, anemia and albuminuria. Roentgenograms showed increased density at the zone of provisional calcification, with an area of rarefaction proximal to this. The long bones showed periosteal thickening, with a dense outer layer and a rarefied inner zone. This patient died, and permission for autopsy was not obtained. His twin brother died suddenly a few days before, during the course of pneumonia. Autopsy showed asphyxia from aspiration of mucus and food into the trachea. Bronchopneumonia was also present. Histologic examination showed extensive metastatic calcification. There was generalized deposition of calcium in the arteries. This took place in the inner layer of the media. There was also calcification in the cardiac muscle. The kidneys showed calcification, which was especially marked in the tubules. Calcification was also present in the lining of the alveoli of the lungs and in the bronchi. The stomach showed deposition of calcium in the muscularis mucosae as well as in the basal portion of the cells comprising the mucosa. The bones were not examined.

These cases illustrate the nutritional and metabolic disturbances caused by vitamin D and the pathologic picture at autopsy. They serve as a warning against overdosage with this powerful agent.

DISCUSSION

DR. T. G. H. DRAKE, Toronto: Will Dr. Ross convert into terms of drops of standard viosterol the dose of vitamin D that these children received?

DR. S. GRAHAM ROSS, Montreal: As I understand it, ordinary viosterol contains 10,000 international (U.S.P.) units per gram. The preparation used contains about 60,000 units per gram, or 2,000 units per drop, with 28 drops to the cubic centimeter. It is much more concentrated.

DR. T. G. H. DRAKE, Toronto: So these children would be getting about 100 to 150 drops daily of ordinary viosterol?

DR. S. GRAHAM ROSS, Montreal: One cubic centimeter of ordinary viosterol would contain about 10,000 units; therefore, these children would be receiving the equivalent of about 60 to 120 drops of such viosterol.

DR. ALTON GOLDBLOOM, Montreal: Were all 4 patients given this preparation of irradiated ergosterol (ostogen)?

DR. S. GRAHAM ROSS, Montreal: Yes.

DR. F. F. TISDALL, Toronto: This report is of tremendous interest from a clinical standpoint. This question of dosage can perhaps be clarified if it is realized that 10 drops of ordinary viosterol (maximum dose) supplies roughly 2,000 units. Dr. Ross said some of these babies received as much as 40,000 units daily. This is twenty times the usual dose. This brings up an important question. The firm which is making this product is out of step with the other firms. Is it advisable to keep up this high potency? A lay person, thinking the preparation was approximately the same as the others, might very readily give a toxic dose. It should be brought to the attention of the manufacturer. One should keep in mind the work that Dr. Drake reported two or three years ago, which showed that 500 units of vitamin D a day (3 or 4 drops of viosterol) completely prevents rickets. The work of Jeans and others in the United States also showed that these doses give the desired effect. The minimum dosage should be 500 units and the maximum 2,000 units.

DR. T. CROSSAN CLARK, Hamilton, Ontario: Did Dr. Ross state that the dose for 1 patient was stepped up from 5 to 15 minims (0.31 to 0.92 cc.)? Why was this change made?

DR. S. GRAHAM ROSS, Montreal: The first case was that of an infant who had whooping cough at 11 months. The child was not gaining weight and not doing well, and the dose was increased to 15 drops (30,000 units). The clinical picture developed after this increase in dosage.

DR. B. BENJAMIN, Montreal: Did you think it advisable to reduce the vitamin D intake of these children who recovered?

DR. S. GRAHAM ROSS, Montreal: The physician in charge of these cases decided, naturally, to keep the dose within normal limits after they completely recovered. I may say in defense of the manufacturers that they specifically state in their directions that the dose is 1 to 2 drops per day. The question certainly arises as to whether it might not be better to fall in line with the ordinary dilution of the concentrates.

Second Session

Saturday Morning, June 17

PRELIMINARY OBSERVATIONS ON DILANTIN THERAPY OF CONVULSIONS. DR. WILLIAM A. HAWKE, Toronto.

(The literature concerning the chemical studies, animal experimentation and clinical reports of Merritt and Putnam was reviewed.) In a series of 24 consecutive cases of convulsions from the Hospital for Sick Children, Toronto, the remedy produced excellent results with grand mal convulsions. In 60 per cent of these a definite improvement over the results of previous medication was seen. With petit mal convulsions the improvement was only 8 per cent over that of previous medication. In this series, 38 per cent showed toxic reactions, consisting chiefly of ataxia, rash and hypertrophy of the gums. None of the reactions was serious. The series is small, and the duration of the observation was short. A further report will be made when the patients have been under treatment for twelve months or longer.

DISCUSSION

DR. ALTON GOLDBLOOM, Montreal: Dr. Hawke's somewhat categoric statement with regard to the effect of dilantin in petit mal perhaps requires a little modification. However, the experience of physicians is rather limited. Therefore it is worth while to record that in my own experience I have cared for 2 children with attacks of petit mal who showed considerable improvement when given dilantin;

one patient a boy of 14 years, had three or four attacks daily, and the other, a boy of 8, had fifteen to twenty attacks daily. The younger child is having only one or two attacks daily, is becoming, according to the mother, much brighter and happier and is able to carry on his work at school. The other is having attacks every two or three days and also, from his own statement, is considerably improved. Experience with this drug is limited, and it should not be discarded entirely for children with petit mal because of one group of unsatisfactory results. Even my own limited experience with 2 cases would encourage me to use the drug further in cases of petit mal.

Dr. P. J. Maloney, Ottawa, Ontario: The drug is prepared in 1 and 1½ grain (0.06 and 0.1 Gm.) capsules. Which dose did Dr. Hawke use?

Dr. S. Graham Ross, Montreal: Does Dr. Hawke space the doses at eight hour intervals throughout the twenty-four hours?

Dr. William A. Hawke, Toronto: As to Dr. Goldbloom's questions regarding the use of this drug in petit mal, my statement may be a bit dogmatic. But I can quote Dr. Stewart, of Parke, Davis & Co., who told me that the general results indicate that petit mal is not as well controlled by dilantin as grand mal. Dr. Pratt, of the Ontario Hospital at Woodstock (for epileptic patients), stated in a letter to me that he controlled attacks of grand mal but petit mal persisted. He used large doses, giving a 0.1 Gm. capsule six or seven times daily. It is interesting to note that of his series of 52 patients, in 10 per cent there developed definitely psychotic manifestations (hypomania, delusions, confused states) and some were definitely assaultive. Of this group only a few had had any behavior disorders before dilantin therapy was started. In reply to Dr. Maloney, the original dose was put up in 0.1 Gm. (1½ grain) capsules. Dr. Stewart has supplied me with new capsules of 0.05 Gm., and also some special 0.03 Gm. capsules for small children. In my series of cases I used 0.1 Gm. capsules. In reply to Dr. Graham Ross, I have just given the medicine with meals and not at particular intervals. I thought probably the slight nausea from the drug would be less at mealtime than at any other time.

Early Introduction of Solid Foods in the Infant Diet. Dr. Doris Monypenny, Toronto.

A study was made of feeding egg yolk, pablum and canned sieved vegetables to infants from the early age of 1 month. No difficulty was experienced in introducing vegetables and pablum. When egg was added, gastrointestinal disturbances occurred in 41 per cent of the cases. When administration of either canned sieved vegetables or pablum was started early, infants were more contented, parents were pleased, and other solids could be added with ease later on. The addition of egg yolk, pablum or canned sieved vegetables did not increase the weight or the hemoglobin content over that of infants receiving milk mixtures alone. Pablum can be added with safety to the infant's diet from the age of 1 month. In many instances the addition of pablum to the diet improved the character of the stools.

DISCUSSION

Dr. Alan Brown, Toronto: It is rather interesting to have observed the changes in infant feeding over a period of twenty-five years. At the beginning of that period one never thought of such early additions of cereals or of vegetables either. It has been my experience during the past few years, just as Dr. Monypenny stated, that cereals and also vegetables can be added earlier, but I have not had the experience of adding either at the age of 1 month, except for specific conditions. There is one question in my mind, however. I think I have seen more cases of potential celiac disease during the past few years, and I have attributed the condition to the too early addition of solid foods. I do not think all infants can be fed in the same way. I recently had an experience with a 13 month old baby from Geneva, Switzerland. I asked the mother what the diet

had been from the age of 4 months. She stated that the doctor in Switzerland had placed the baby on a regimen of three scraped apples, two oranges and thirteen bananas a day. The baby had had an almost continuous intestinal disturbance since that time and now presents the typical aspect of celiac disease. In private practice I should certainly feel a little apprehensive of feeding all babies vegetables as early as Dr. Monypenny did, but I have not the same feeling about pablum. However, sometimes it causes some looseness of the bowels, which may necessitate a change to a more refined cereal.

Dr. A. Goldbloom, Montreal: I think that when pediatricians discuss the addition of solid foods they lose sight of the fact that the children are taking solid food from the time they are first fed because no food is more solid than coagulated milk. The distinction is more apparent than real. "The addition of foods other than milk" is a better way to put it. This addition has been going on since 1917, when Eddy and Roper added finely ground pancreas to the diet of very young infants (4 to 6 weeks of age). Sauer first commenced his method of thick feeding for pyloric stenosis and pylorospasm a little later. A few years after this, Ross and Scriver made a study of the feeding of bananas to young infants, and they showed that banana can be given at an early age. The food must be so finely divided that the baby can take it. Beyond that it is only a question of the infant's tolerance, and that varies. Tolerance is less for egg than for other foods. Sometimes infants cannot take egg during the first and second years of life. If the baby can eat egg, he can take it at any age. Physicians have been a little diffident in the matter of adding other foods. It would be an advantage to feed a greater variety of foodstuffs because of the minerals and vitamins that the child would receive. The food problem seems to be a matter of tolerance on the one hand and of fine division on the other; with this understood, there is no food that cannot be considered.

Dr. R. R. MacGregor, Kingston, Ontario: Dr. Monypenny's paper brings up a subject that is being much discussed at the present time, particularly in America. Hendee Smith, of New York, deplored what he termed the pernicious practice of the early addition of foods to infants' diets. He pointed out that in his experience, which has extended over a great many years, he has noted a number of cases of intestinal disturbance of chronic types, such as celiac disease, or kindred diseases, in which fats are fairly well absorbed. These children suffer from indigestion. Other observers have expressed this same opinion.

Dr. Doris Monypenny, Toronto: Some of the children in the groups have been followed almost to the age of 2 years, and there have been no subsequent gastrointestinal disturbances.

Treatment of Chronic Eczema in Children. Dr. John R. Ross, Dr. H. E. Edwards and Dr. J. F. McCreary, Toronto.

Twenty-eight patients with chronic allergic eczema who were previously unsuccessfully treated with local applications have been observed over a three year period. In 73 per cent of the cases, a family history of allergy was obtained. The patients were tested by the intradermal and scratch methods, and patch tests were made in certain cases. Sensitization to wheat was found to be the most common type of food allergy, and a special elimination diet was used in treating the food-sensitive children. Of 18 patients showing positive reactions to foods, contactants and inhalants, 9 were cured and only 4 failed to show improvement in one year. Of 6 children who reacted negatively to cutaneous tests, 4 were cured in one year. Three of the 4 patients with contact dermatitis were cured by the removal of silk and wool and of the other materials to which they reacted.

DISCUSSION

Dr. N. Silverthorne, Toronto: I was interested in some of the recent work with elimination diets in a New York hospital. It was pointed out how difficult it is to eliminate from the diet the food materials to which the child is sensitive.

For instance, in a case of sensitivity to egg, each time the child had egg, asthma developed. Egg was eliminated as well as possible, and about two months later the child had another attack of asthma. It was found that he had had some clear jelly beans coated with egg white.

COMPARATIVE INCIDENCE OF INFECTIONS IN BREAST FED AND ARTIFICIALLY FED INFANTS. DR. J. H. EBBS and DR. FRANCES MULLIGAN, Toronto.

In reviewing the case histories of 1,500 infants under 1 year of age who were admitted with infections to the Hospital for Sick Children during the past three and a half years, it was found that fewer breast-fed babies were admitted with infections than artificially fed babies. The incidence of breast feeding among the 1,500 babies with infections was less than half the incidence of breast feeding in the Well Baby Clinics in the city. Infections of the respiratory tract were found more frequently than other infections. The incidence of gastrointestinal infections was lower in the breast-fed babies. The mortality was slightly higher in the breast-fed group. The mortality for babies receiving adequate amounts of cod liver oil and orange juice was 11.9 per cent as compared with 18.8 per cent for those who did not receive adequate vitamin therapy. Only 38.4 per cent of the babies admitted with infections were getting cod liver oil and orange juice, while 83.1 per cent of the babies attending Well Baby Clinics were receiving adequate amounts.

DISCUSSION

DR. F. F. TISDALL, Toronto: One can learn definite lessons from this paper. As Dr. Ebbs carefully pointed out, these figures apply only to artificially fed and breast-fed infants admitted to a hospital, but even so the mortality figures are so different from those reported by Dr. Grulee of Chicago that they deserve attention. Once the babies came into the hospital there was no essential difference in the course of their disease because of breast feeding or artificial feeding. Another important point is the striking lack of adequate administration of vitamins C and D to the babies coming into the hospital as compared with those attending the Well Baby Clinics in the city. In these clinics 83 per cent of the infants were looked after in this regard, but of the group admitted to the hospital only 35 per cent had received these vitamins. It was thought that education of the public had solved this problem; it is rather a shock to find out that two thirds of the babies coming into the hospital have not been getting the vitamins that were supposedly being adequately administered. Educational efforts along these lines must be not only continued but increased.

DR. ALAN BROWN, Toronto: In 1917 my co-workers and I made a survey of breast feeding in the children of Toronto. We found by questioning nurses, students and physicians that twenty-five years previously the incidence of breast feeding was much higher than in 1917. Three years ago I collected the statistics from the child welfare clinics in the city of Toronto and analyzed them; I found a considerable decrease in the amount of breast feeding. That took place over a period in which the number of pediatricians had increased (1936 as compared with 1917). Last year I had a record kept of the feedings of the babies born in the private patients' pavilion of the Toronto General Hospital. Of the babies supervised by pediatricians, roughly speaking, 20 per cent were breast fed when they left the hospital and 80 per cent were receiving artificial feeding. Among those supervised by obstetricians, family physicians or the nurse in charge, 85 to 90 per cent were breast fed when they went home. A considerable change has taken place in the attitude of the modern pediatrician. It is too easy to feed these babies artificially, and the mother prefers it as it is less trouble than continuing to feed the baby by the breast. This fact should be borne in mind by pediatricians. We have all fallen into the mistake of weaning a baby for too insignificant reasons. We all know that breast feeding certainly increases resistance to infection. Babies receiving breast milk hardly ever have any serious illness. Pediatricians are largely responsible for the decreased incidence of breast feeding.

DR. J. H. EBBS, Toronto: With reference to Dr. Tisdall's remarks, we are going to try to find out why a large number of babies admitted to the hospital have not been attending the Well Baby Clinics.

AIR CONTAMINATION AND AIR STERILIZATION. DR. E. CHANT ROBERTSON, Toronto, and others.

This paper is published in full in this issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 1023.

THE MENINGOCOCCUS AND MENINGOCOCCIC INFECTION. DR. N. SILVERTHORNE, Toronto.

A study was made of 51 patients with the three clinical types of meningococcic meningitis. In 40 cases of the acute type the mortality was 14 per cent. Complications were frequent; hydrocephalus occurred in 9 instances. Gram-negative diplococci were found in blood smears of the purpuric lesions of 6 patients. Forty-two families of the patients were visited. Material was collected from contacts by swab, and environmental conditions were investigated. In these families, 327 contacts were examined for the presence of the meningococcus in the nasopharynx, and 102 (or 31 per cent) of the cultures were positive. In 33 of the 42 families, one or both parents were found to be harboring meningococci.

During four and one-half years of the seven year study, 2,378 nasopharyngeal swabs were examined from an average of 50 persons monthly. No less than 20 per cent of these yielded the meningococcus. Of organisms from the contact carriers and patients, 94 per cent of the strains examined were found to possess varying degrees of virulence.

Of organisms from the noncontact carriers, only approximately 30 per cent were found to be virulent.

The disease as it occurred in children in Toronto in its sporadic form was mainly due to the type II meningococcus.

DISCUSSION

DR. E. CHANT ROBERTSON, Toronto: I did not fully understand what Dr. Silverthorne meant when he said that one could not draw conclusions from the fact that 14 per cent of those treated with antimeningococcus serum died. Was this a poor form of treatment?

DR. N. SILVERTHORNE, Toronto: I did not want to go into too much detail. It is difficult to evaluate the effects of any form of treatment in a small series or even, for that matter, in a large series of cases. Antimeningococcus serum is mainly active against infection with type I meningococci. It has agglutinins for type II organisms but no highly protective antibodies. Before proper evaluation of any treatment can be made, alternate cases must be studied with various methods of treatment. The rise of the bactericidal power in the blood of the patient must be analyzed, and the virulence of the infecting micro-organism must be measured in each case.

CARDIAC IRREGULARITIES IN INFANTS. DR. A. GOLDBLOOM and DR. H. N. SEGAL, Montreal.

Attacks of auricular paroxysmal tachycardia in young infants have been reported in the literature only twenty times. Such attacks have been noted more frequently in older children. Two such cases are reported. In a third case auricular fibrillation was observed in an infant 6 months of age, in whom the condition probably had been present from birth.

The cause is unknown. The suggestion of an allergic cause in some cases is made because such an association has been proved for some adults. Treatment consists of pressure on the eyeball and on the carotid sinus, the production of vomiting and the administration of acetylcholine, morphine sulfate and digitalis.

DISCUSSION

DR. J. D. KEITH, Toronto: Since last summer I have observed an interesting case of paroxysmal tachycardia with some unusual features. A 12 year old boy who attends school seems to have almost continuous paroxysmal tachycardia, with a pulse rate varying between a normal value and 150. Some irregularity was noticed when he was 7 years of age. The condition may be congenital in origin, but the boy has certainly had it for the last five years. It is apparently due to an ectopic focus in the auricle and gives rise to inverted P waves. About every fifteen beats the heart returns to normal behavior for two or three beats. The sounds suggest simple tachycardia with occasional irregular beats. Actually the tachycardia is due to the abnormal rhythm, and the sudden slowing for a few beats is a temporary return to normal. The family has known about this for some time, and they have tried to keep the child quiet. However, he sometimes walks about 4 miles (6.4 kilometers) a day and he seems to be in good general condition. The cardiac abnormality does not interfere with his usual activity. I was interested in Dr. Goldbloom's comments on treatment. I have observed another case recently. A girl about 12 years of age had several attacks before the last persistent one, which lasted two weeks. Nearly every form of treatment was used, including small doses of acetylcholine. I had given it to some normal children, in whom about 0.5 mg. was enough to produce first an elevation in the pulse rate and after a few minutes a slight drop. I feel that much larger doses are dangerous. I notice that in a case reported from New York 5 mg. produced asystole. I do not think that atropine works rapidly enough in these cases to make one feel safe with the drug. If given subcutaneously, it takes ten minutes or longer to reach its full effect. It would be better given intravenously. If an overdose of acetylocholine were given, the patient would either die or recover before the atropine could take effect. I should be interested to know what dose of acetylcholine Dr. Goldbloom used.

DR. A. GOLDBLOOM, Montreal: One milligram.

DR. S. GRAHAM ROSS, Montreal: Some years ago I observed a woman in labor in whom the fetus showed signs of distress. The obstetrician found that the pulse rate of the fetus was well over 200, so he induced labor. I saw the child two hours after birth; at that time it had typical paroxysmal tachycardia, but the inference is fairly clear that it had developed prenatally. Repeated attacks were observed for some months. I have since lost track of the child.

Book Reviews

Seelischer Gesundheitsschutz. By Heinrich Meng. Price, 8 fr., paper. Pp. 223, with 3 illustrations. Basel: Beno Schwalbe & Co., 1939.

The mental hygiene movement is slowly entering into middle age. In the thirty odd years of its existence a voluminous literature has accumulated, the nature of which—to put it broadmindedly—is deserving of much criticism and perhaps as much praise. The qualifications for authorship have up to now at least been unlimited. Psychiatrists, being familiar with the development of the central nervous system and the possible deviations from normal function of its various parts, naturally have been cautious in their "educational campaigns" for mental health. Child guides and social workers on the other hand, with their lack of practical knowledge of physiology and just enough understanding of psychology to rush in where the proverbial "angels fear to tread," have stopped at little or nothing in their attempt to spread the gospel of mental hygiene. The results of this dilemma are known to every pediatrician.

The book under present consideration offers a ray of hope. In the first place it was written by an authority on the subject. Professor Meng is one of the leading psychiatrists on the European continent. For years he has devoted much time and energy to the study of the emotional processes of childhood. Secondly, the book is written in scientific rather than in sentimental style, which is an important departure from the prevailing system in this hitherto pseudomedical field.

The contents are well arranged in three main parts: (1) a general discussion of diagnosis, prophylaxis and hygiene; (2) a study of the emotional processes and their relation to organic disease, and (3) case histories illustrating the beneficial application of the principles of mental hygiene to the various age periods.

The Infant and Child in Health and Disease. Reference to Nursing Care. By John Zahorsky, M.D., and Elizabeth Noyes, R.N. Price, $3.00. Pp. 496, with 140 illustrations. St. Louis: C. V. Mosby Company, 1939.

This is the second edition of this book, but it has been entirely rewritten to meet the new curriculum adopted by the National League of Nursing Education. For this reason it is especially a book for student nurses in nursing schools. It is divided into three parts. The first part deals with the normal infant and child, and this is not a tiresome reiteration of old subjects but what the authors believe is most useful to the trained nurse. Part 2 describes the technical work in the treatment of diseases of infants and children. This includes work both in the home and in the hospital. Part 3 outlines and describes the various procedures used in the technical care of infants.

The book is well written, and the illustrations are excellently chosen. It should be of advantage to the student as well as to the graduate nurse and should be in the library of every hospital training school for nurses.

Nursing Mental Diseases. By Harriet Bailey, R.N. Fourth edition. Price, $2.50. Pp. 264. New York: The MacMillan Company, 1939.

This is a well written volume describing the most common mental disorders and the therapeutic technic used. It was written for nurses by a nurse with wide experience. It should be of great value as a textbook for student nurses or for any nurse who takes care of psychopathic patients in hospitals.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Prof. Luigi Spolverini, Policlinico Lungo Tevere Melini 24, Rome, Italy.
Secretary: Professor Vitetti, Rome, Italy.
Place: Boston. Time: Sept. 3-5, 1940.
American Committee:
Chairman: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, 300 Longwood Ave., Boston.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Sociedad Cubana de Pediatría

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: New York. Time: June 10-14, 1940.

American Academy of Pediatrics

President: Dr. H. F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Netherland Plaza Hotel, Cincinnati. Time: Nov. 16-18, 1939.
Region I. Place: Mayflower Hotel, Washington, D. C. Time: April 4-6, 1940.
Region II. Place: Edgewater Gulf Hotel, Edgewater Park, Miss. Time: March 22-23, 1940.
Region IV. Place: Seattle, Wash. Time: May 30-June 1, 1940.

American Hospital Association, Children's Hospital Section

Chairman: Miss Mabel Binner, Children's Memorial Hospital, Chicago.
Secretary: Winifred Culbertson, Children's Convalescent Hospital, Cincinnati.

American Pediatric Society

President: Dr. Herbert B. Wilcox, 39 E. 75th St., New York.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.

Canadian Society for the Study of Diseases of Children

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

Society for Pediatric Research

President: Dr. Daniel C. Darrow, 330 Cedar St., New Haven, Conn.
Secretary: Dr.Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Frederick Fischer, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. C. L. Lyons, Paulsen Medical-Dental Bldg., Spokane, Wash.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. John Schoonover, Republic Bldg., Denver.
Secretary: Dr. F. Craig Johnson, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Hughes Kennedy Jr., Highland Plaza Apts., Birmingham, Ala.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.
Place: Memphis, Tenn. Time: Nov. 21-24, 1939.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. Stewart H. Welch, 1117 S. 20th St., Birmingham.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. G. D. Murphy, 112 Peach St., El Dorado.
Secretary: Dr. Madeline M. Melson, 909 Main St., Little Rock.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Harold K. Faber, 2341 Clay St., San Francisco.
Secretary: Dr. Hartzel H. Ray, 23–2d Ave., San Mateo.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

GEORGIA PEDIATRIC SOCIETY

President: Dr. L. H. Muse, 384 Peachtree St. N. E., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Scientific Meeting: Place: Atlanta. Time: December 1939. Business Meeting: Place: Savannah. Time: April 1940.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. C. V. Calvin, 144 Golden Hill St., Bridgeport.
Secretary: Dr. E. T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. O. N. Torian, 23 E. Ohio St., Indianapolis.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. Phillip C. De Verges, Audubon Bldg., New Orleans.
Secretary-Treasurer: Dr. W. C. Rivenbark, 220 Physicians and Surgeons Bldg., New Orleans.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester.
Secretary: Dr. Leslie O. Ashton, 842 Park Ave., New York.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. John M. Higgins, 600 S. Wilbur Ave., Sayre.
Secretary: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Allan L. Richardson, 3001 W. Grand Blvd., Detroit.
Secretary: Dr. Ward L. Chadwick, 524 Medical Arts Bldg., Grand Rapids.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Secretary-Treasurer: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Place: To be designated by society. Time: Yearly.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. Herman M. Jahr, 1120 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Marion Y. Keith, 369 N. Elm St., Greensboro.
Secretary: Dr. G. W. Kutscher Jr., 176 Woodfin St., Asheville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Ben H. Nicholson, 301 W. 12th St., Oklahoma City.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. D. Lesesne Smith Jr., 187 Oakland Ave., Spartanburg.
Secretary-Treasurer: Dr. William Weston Jr., 1428 Lady St., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. William E. Van Order, 546 McCallie Ave., Chattanooga.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.

TEXAS PEDIATRIC SOCIETY

President: T. A. Tumbleson, 2100 North St., Beaumont.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Fort Worth. Time: Oct. 14, 1939.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. W. Ambrose McGee, 616 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, Medical Arts Bldg., Roanoke.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. J. L. Blanton, 207 Fairmont Ave., Fairmont.
Secretary: Dr. Theresa O. Snaith, 450 Center Ave., Weston.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. N. C. Wetzel, 2103 Adelbert Rd., Cleveland.
Secretary: Dr. Fred Rittenger, 10515 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. T. B. Verner, 170 St. George St., Toronto, Canada.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. Samuel T. Levethan, 254 E. 184th St., Grand Concourse, New York.
Secretary: Dr. David Greene, 910 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Benjamin Kramer, 6 Pierrepont St., Brooklyn.
Secretary: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Gerard N. Krost, 2376 E. 71st St., Chicago.
Secretary: Dr. George F. Munns, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

DALLAS PEDIATRIC SOCIETY

President: Dr. Harold Nesbit, 1719 Pacific Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. William O'Donnell, 1553 Woodward Ave., Detroit.
Secretary: Dr. Robert Mason, 5140–2d Blvd., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

FULTON COUNTY MEDICAL SOCIETY, PEDIATRIC SECTION (ATLANTA, GA.)

Chairman: Dr. L. H. Goldsmith, 384 Peachtree St. N. E., Atlanta.
Secretary: Dr. James P. Hanner, 384 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

HOUSTON PEDIATRIC SOCIETY

President: Dr. James H. Park Jr., 3717 Main St., Houston, Texas.
Secretary-Treasurer: Dr. Thomas J. Donovan, 2418 Travis St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Urban Busiek, 200 E. Pershing St., Springfield, Mo.
Secretary: Dr. Fred Speer, 2700 Parallel Ave., Kansas City, Kan.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. H. R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Paul M. Hamilton, 248 E. Main St., Alhambra, Calif.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd.
Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Benjamin Stoloff, 1149 Eastern Parkway, Brooklyn.
Secretary: Dr. Harry Apfel, 988 Park Pl., Brooklyn, N. Y.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., second Monday of each month, October to March, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. James Dobbins, 42-04 Ditmars Blvd., Long Island City, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry H. Donnally, 1612 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. Harry A. Spigel, 2647 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of October, January, February, March and April.

Memphis Pediatric Society

President: Dr. Barton Etter, 376 S. Bellevue St., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. Helen Jane Zillmer, 781 N. Jefferson St., Milwaukee.
Secretary-Treasurer: Dr. Samuel E. Kohn, 425 E. Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Lucy Porter Sutton, 168 E. 74th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northwestern Pediatric Society

President: Dr. Robert Rosenthal, 437 Lowry Medical Arts Bldg., St. Paul.
Secretary-Treasurer: Dr. R. E. Nutting, 205 W. 2d St., Duluth, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Time: Every month, except June, July and August.

Philadelphia Pediatric Society

President: Dr. Samuel Goldberg, 4546 N. Broad St., Philadelphia.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. James LeRoy Foster, Highland Bldg., Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., first Thursday of each month, except July, August and September.

Rochester Pediatric Society

President: Dr. David Wolin, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. H. C. Soule, 16 N. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Second Friday of each month.

St. Louis Pediatric Society

President: Dr. Ralph L. Cook, 508 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: Third Friday of each month from September to June.

Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. E. Earl Moody, 829 S. Alvarado Ave., Los Angeles.
Secretary: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Clement Smith, 1101 Beacon St., Brookline, Mass.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. Norman Survis, 650 Main St., New Rochelle.
Secretary-Treasurer: Dr. Elvira Ostlund, 131 Purchase St., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.